#9

U.S. Patent No. 4,559,334

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent No. 4,559,334

Issued : December 17, 1985

Patentees : Takao Takaya
Hisashi Takasugi
Takashi Masugi
Hideaki Yamanaka
Kohji Kawabata

For : 7-SUBSTITUTED-3-VINYL-3-CEPHEM COMPOUNDS AND PROCESSES FOR PRODUCTION OF THE SAME

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF AN APPLICATION

FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for the Product Omnicef® (cefdinir capsules), the NDA for which was approved on December 4, 1997.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

[X] A prescribed fee in the amount of $ 1,120.00 is required for the application presented.

Please charge Deposit Account No. 23-0455 in the amount of the prescribed fee above, or such greater or lesser amount as the Commissioner determines is required by law. This letter is submitted in triplicate for deposit account purposes.

Respectfully submitted,

January 26, 1998
Date

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
Pharmaceutical Patents
WARNER-LAMBERT COMPANY
Parke-Davis Pharmaceutical
Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
Tel: (313) 996-5215
Fax: (313) 996-1553

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 with Declaration and attachments thereto.

[X] A certified DUPLICATE APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] This Transmittal Form in triplicate for deposit account purposes.

[X] Return Post Card.

CAD01238.045

#9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Number: 4,559,334

Patentees : Takao Takaya
Hisashi Takasugi
Takashi Masugi
Hideaki Yamanaka
Kohji Kawabata

Issue Date: December 17, 1985

Title: 7-SUBSTITUTED-3-VINYL-3-CEPHEM COMPOUNDS AND PROCESSES FOR PRODUCTION OF THE SAME

APPLICATION FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. §156

January 26, 1998
Date Mailed

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

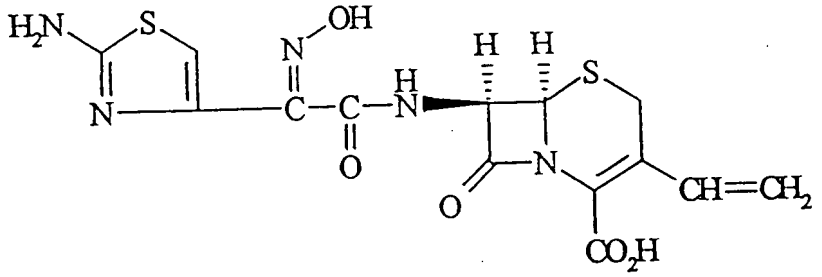
Pursuant to §201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains New Jersey, 07950, as agent for Fujisawa Pharmaceutical Company, Ltd., the assignee of record, hereby requests an extension of 1601 days to the 17 year term of United States Patent No. 4,559,334, thereby setting expiration to May 6, 2007.

A letter from the assignee authorizing Warner-Lambert Company to submit this application is attached as Exhibit 1 (AUTHORIZATION LETTER).

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is Omnicef® (cefdinir capsules). The active ingredient in Omnicef® is cefdinir. Omnicef® is a cephalosporin antibiotic and is approved for treatment of bacterial infections. Chemically, Omnicef® (cefdinir) is [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Another name for cefdinir is 7-[2-(2-aminothiazol-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3- cephem-4-carboxylic acid (syn isomer). The empirical formula of cefdinir is $C_{14}H_{13}N_5O_5S_2$; its molecular weight is 395.42; and its chemical structure is:



Cefdinir is a white to slightly brownish yellow or off-white crystalline powder that is practically insoluble in water, and slightly soluble in dilute hydrochloric acid.

Omnicef® (cefdinir capsules) is also known within Warner-Lambert Company as "CI-983", "FK-482" and "PD-134393", and has been assigned CAS registry No. 91832-40-5.

Omnicef® is a pharmaceutical in the form of capsules for oral delivery to patients suffering from community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections. Omnicef® capsules contain 300 mg of cefdinir. Omnicef® is further described in the sections titled DESCRIPTION of the Package Insert, (Exhibit 2) (PACKAGE INSERT) which is the Product Information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review of Omnicef® (cefdinir capsules) occurred under §505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §355. Section 505 provides for the submission and approval of new drug applications ("NDAs"). The original submission was under §507(b) for antibiotic drug products meeting the definition of "antibiotic drug" under 21 U.S.C. §357(a). That section was repealed by the FDA Modernization Act of 1997, and antibiotics are now "drugs" subject to review under §505.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Omnicef® (cefdinir capsules) was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FFDCA on December 4, 1997; see Exhibit 3 (APPROVAL LETTER).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in Omnicef® is cefdinir. Neither cefdinir, as the free acid, nor any salt or ester of cefdinir free acid, has previously been approved.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f) and an identification of the date of the last day on which the application could be submitted.

The Omnicef® (cefdinir capsules) product was approved for commercial marketing on December 4, 1997, and the last day within the sixty day period permitted for submission of an application for extension of the patent is February 1, 1998. The date of submission of the present application is no later than February 1, 1998, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NUMBER:	4,559,334
INVENTORS:	Takao Takaya Hisashi Takasugi Takashi Masugi Hideaki Yamanaka Kohji Kawabata
Issue Date:	December 17, 1985
Expiration Date:	December 17, 2002

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent No. 4,559,334 is attached as Exhibit 4 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

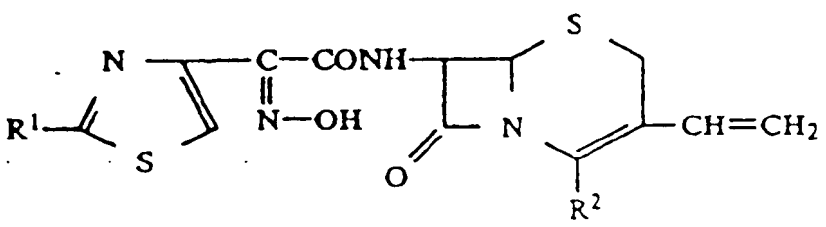
No disclaimer, certificate of correction or reexamination certificate has been issued for U.S. patent No. 4,559,334. A copy of a status report showing the first, second, and third maintenance fees (4^{th}, 8^{th} and 12^{th} year fees) being paid for U.S. Patent No. 4,559,334 is attached as Exhibit 5 (MAINTENANCE FEE RECEIPTS).

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

U.S. Patent No. 4,559,334 claims the FDA approved product Omnicef® (cefdinir capsules) as a new chemical entity in Claims 1-3, and as a pharmaceutical composition in Claim 20.

Claims 1-3, and 20 are set forth below:

1. A syn isomer of the compound of the formula:



(I)

in which

R^1 is amino or a protected amino group, and

R^2 is carboxy or a protected carboxy group,

and a pharmaceutically acceptable salt thereof.

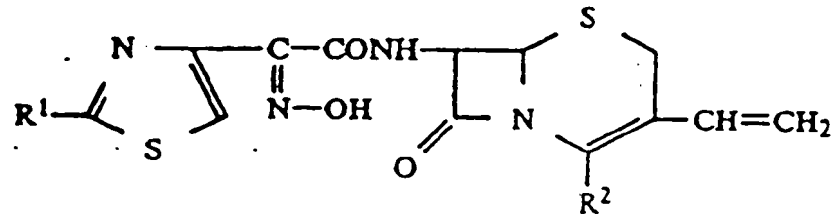
2. A compound of claim 1, wherein R^1 is amino.

3. A compound of claim 2, which is 7-[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) or its sodium salt or its potassium salt.

20. A pharmaceutical antimicrobial composition which comprises an antimicrobially effective amount of a compound of claim 1 and a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

Regarding Claim 1

Claim 1 reads, in part, "A syn isomer of the compound of the formula:



(I)

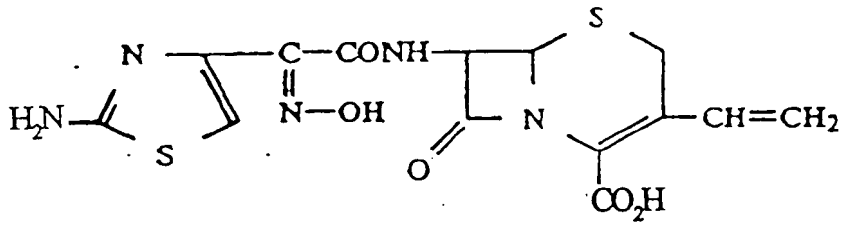
in which

R^1 is amino..., and

R^2 is carboxy...."

Omnicef® (cefdinir capsules) is a cephalosporin having formula I wherein R^1 is amino and R^2 is carboxy.

Omnicef® (cefdinir capsules) thus has the specific chemical structure



Regarding Claim 2

Claim 2 requires "A compound of Claim 1, wherein R^1 is amino". Omnicef® is a cephalosporin compound of structural formula I of Claim 1, wherein R^1 is amino.

Regarding Claim 3

Claim 3 requires "A compound of Claim 2, which is 7-[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)...." This is the active ingredient in Omnicef® (cefdinir capsules).

Regarding Claim 20

Claim 20 requires "A pharmaceutical antimicrobial composition which comprises an antimicrobially effective amount of a compound of Claim 1...in admixture with pharmaceutically acceptable carriers."

Omnicef® (cefdinir capsules) is a cephalosporin antimicrobial drug product having the formula recited in Claim 1, admixed with pharmaceutically acceptable carriers, including carboxymethylcellulose calcium, NF; polyoxyl 40 stearate, NF; magnesium stearate, NF; and silicon dioxide, NF.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

On April 30, 1990, the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company (the exclusive licensee of Fujisawa Pharmaceutical Co. Ltd.) submitted to the Food and Drug Administration an Investigational New Drug Application (IND) for cefdinir. A copy of the letter accompanying the IND submission is Exhibit 6 (IND SUBMISSION LETTER). The cover letter identified cefdinir as "CI-983 Capsules". The IND was received by the FDA on May 2, 1990, and was assigned IND number 34,738. The IND became effective on June 1, 1990, (30 days after receipt) as

evidenced by Exhibit 7 (IND ACKNOWLEDGMENT LETTER) attached hereto. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1) as June 1, 1990.

On September 3, 1996, a new drug application was submitted under §507 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and §314.50 of Title 21 Code of Federal Regulations for Omnicef® (cefdinir capsules) by the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company. A copy of the cover letter attached to the NDA of September 3, 1996, is submitted herewith as Exhibit 8 (NDA SUBMISSION LETTER). The NDA was received by the FDA on September 4, 1996 and assigned number 50-739 Exhibit 9, (NDA RECEIPT LETTER).

The NDA was approved on December 4, 1997. Attached as Exhibit 3 (APPROVAL LETTER) is a copy of a letter dated December 4, 1997, from the FDA to Parke-Davis division of Warner-Lambert Company approving the NDA 50-739 for the product Omnicef® (cefdinir capsules).

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. §156(g)(1), the date of the first approval of Omnicef® (cefdinir capsules) is December 4, 1997.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), the IND for Omnicef® became effective on June 1, 1990. The clinical studies under the IND are summarized in the attached Exhibit 10 (IND LOG). The IND LOG establishes that Warner-Lambert Company, through its Parke-Davis Pharmaceutical Division, worked in close consultation with the FDA, prepared detailed clinical protocols for evaluating cefdinir, conducted clinical trials and accumulated efficacy and safety data needed to support marketing approval of Omnicef® (cefdinir capsules). These clinical studies were used to support NDA 50-739 submitted by Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company on September 3, 1996.

Subsequent to the submission of the NDA, WARNER-LAMBERT COMPANY had numerous contacts and meetings with the FDA with respect to the application and these are summarized in the attached Exhibit 11 (NDA LOG).

Both Exhibit 10 and Exhibit 11 have been redacted to remove confidential and non-essential information.

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension Under 35 U.S.C. §156(a)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described by corresponding number, each of these elements is satisfied here:

(1) The statutory term of U.S. Patent No. 4,559,334 expires on December 17, 2002 (seventeen years from issue date). The present Application has, therefore, been submitted before the expiration of the patent term. All required maintenance fees have been paid. (See Exhibit 5).

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This Application is submitted by Warner-Lambert Company, as authorized agent (Exhibit 1, AUTHORIZATION LETTER) for Fujisawa Pharmaceutical Co., Ltd., the owner of record of Patent 4,559,334, by assignment recorded at Reel 4456, Frames 0106 - 0107 (see Exhibit 12, (ASSIGNMENT RECORDATION)) This Application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date, December 4, 1997, that the Omnicef® (cefdinir capsules) product received permission for marketing under the Federal Food, Drug, and

Cosmetic Act, and ending on February 1, 1998, and contains the information required under 35 U.S.C. § 156(d).

(4) As evidenced by the letter from the FDA dated December 4, 1997, Exhibit 3, (APPROVAL LETTER) the Omnicef® (cefdinir capsules) product was subject to a regulatory review period under § 505 of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of Omnicef® (cefdinir capsules) after regulatory review under §505 is the first permitted commercial marketing of cefdinir, the active ingredient in the Omnicef® (cefdinir capsules) approved product. This is confirmed by the absence of any approved new drug application under which Omnicef® (cefdinir capsules) could be commercially marketed prior to December 4, 1997.

Statement as to Length of Extension Claimed
In Accordance With 37 C.F.R. §1.775

The term of U.S. Patent No. 4,559,334 should be extended for a period of 1601 days to May 6, 2007.

The period of extension is determined in accordance with 35 U.S.C. §156 and follows the format set forth in 37 CFR §1.775(c) and (d).

37 CFR §1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. §156(g)(1)(B), it is the sum of --

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

The number of days between the effective date of the IND, June 1, 1990, and the

initial receipt of the NDA, September 4, 1996, is a period of 2288 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of the NDA, September 4, 1996, to NDA approval, December 4, 1997, is a period of 457 days.

37 C.F.R. § 1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on June 1, 1990, which were on or before the date on which the patent issued, December 17, 1985, is a period of 0 days.

2288 days minus 0 days equals 2288 days;

AND

the number of days in the period of the NDA, received on September 4, 1996, which were on or before the date the patent was issued, December 17, 1985, is a period of 0 days.

457 days minus 0 days is 457 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. §156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

Applicant submits it was diligent in all matters involving Omnicef® (cefdinir capsules) and accordingly the number of days applicant did not act with due diligence is 0 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2288 days equals 1144 days. (Thus, U.S. Patent No. 4,559,334 should be entitled to an extension of 1601 days (1144 IND period plus 457 NDA period)).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 1601 days to December 17, 2002, the original term of the patent (no terminal disclaimer was made), extends the term to May 6, 2007.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to December 4, 1997, the date of approval of the NDA, gives the date of December 4, 2011.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is May 6, 2007.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer;

Adding 5 years to the original expiration date of the patent (December 17, 2002) gives the date of December 17, 2007.

and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date:

Comparing May 6, 2007, and December 17, 2007, the earlier date is May 6, 2007, and the patent term should therefore be extended to May 6, 2007.

(6) If the original patent was issued before September 24, 1984,

This is not applicable for the patent.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Applicant is unaware of any additional information material to this Application for extension.

(14) Prescribed Fee:

The prescribed fee of $1,120.00 for receiving and acting on this application for extension of patent term is hereby authorized. Please charge Deposit Account No. 23-0455 in the amount of the fee above, or such greater or lesser amount as the Commissioner determines is required by law.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
Pharmaceutical Patents
WARNER-LAMBERT COMPANY
Parke-Davis Pharmaceutical
Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
Tel: (313) 996-5215
Fax: (313) 996-1553

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. §1.740.

DECLARATION

I, Charles W. Ashbrook, hereby declare that I am authorized on behalf of FUJISAWA PHARMACEUTICAL CO., LTD., the owner of record of U.S. Patent 4,559,334, to apply for an extension of the term of U.S Patent No. 4,559,334. I further declare that: I have reviewed and understand the contents of this Application being submitted pursuant to 35 U.S.C. § 156; I believe the patent is eligible for extension pursuant to 37 C.F.R. § 1.710; I believe that the length of extension claimed in this Application is fully justified under 35 U.S.C. § 156 and the applicable regulations; and I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,559,334.

WARNER-LAMBERT COMPANY

Date: January 26, 1998 By: Charles W Ashbrook

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
Pharmaceutical Patents
WARNER-LAMBERT COMPANY
Parke-Davis Pharmaceutical
Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
Tel: (313) 996-5215
Fax: (313) 996-1553

EXHIBIT 1

AUTHORIZATION LETTER

Fujisawa Pharmaceutical Co., Ltd.
Intellectual Property
1-6, Kashima 2-chome, Yodogawa-ku, Osaka 532, Japan
Telephone : 06-390-1225~9
Facsimile : 06-304-1264

Fujisawa

Exhibit 1

[Name]

[Date]

Via

Assistant Commissioner for Patents
Washington, D.C. 20231

Re : Application for Extension of United States Patent No. 4,559,334

United States Patent No. 4,559,334 is assigned to Fujisawa Pharmaceutical Company, Ltd. The assignment is recorded at Reel 4456, Frame 0106 in the United States Patent and Trademark Office.

Fujisawa Pharmaceutical Company, Ltd., as record owner of the entire right, title and interest in United States Patent No. 4,559,334 hereby appoints Warner-Lambert Company as its agent for the purpose of filing an application for extension of the term of United States Patent No. 4,559,334 under 35 U.S.C. § 156, and hereby grants a Power of Attorney to the following individuals for purposes of filing and prosecuting the application for extension:

Charles W. Ashbrook	Registration No. 27,610
Todd M. Crissey	Registration No. 37,807
Francis J. Tinney	Registration No. 33,069

Fujisawa Pharmaceutical Company, Ltd.

By: Yoshikazu Nishide

Name: Yoshikazu Nishide

Title: Director, Intellectual Property

EXHIBIT 2

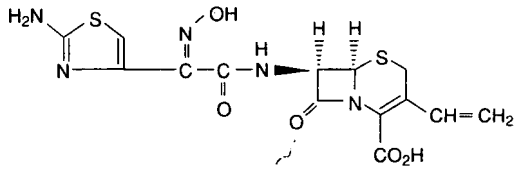
PACKAGE INSERT

0067G050
Omnicef®

Omnicef® (Cefdinir) Capsules
Omnicef® (Cefdinir) for Oral Suspension

DESCRIPTION

OMNICEF® (cefdinir) Capsules and OMNICEF® (cefdinir) for Oral Suspension contain the active ingredient cefdinir, an extended-spectrum, semisynthetic cehalosporin, for oral administration. Chemically, cefdinir is [6R-[6α,7β (Z)]]-7-[[(2-amino-4-thiazolyl)-(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Cefdinir is a white to slightly brownish-yellow solid. It is slightly soluble in dilute hydrochloric acid and sparingly soluble in 0.1 M pH 7.0 phosphate buffer. The empirical formula is $C_{14}H_{13}N_5O_5S_2$ and the molecular weight is 395.42. Cefdinir has the structural formula shown below:



OMNICEF Capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, NF; polyoxyl 40 stearate, NF; magnesium stearate, NF; and silicon dioxide, NF. The capsule shells contain FD&C Blue #1; FD&C Red #40; D&C Red #28; titanium dioxide, NF; gelatin, NF; and sodium lauryl sulfate, NF.

OMNICEF for Oral Suspension, after reconstitution, contains 125 mg cefdinir per 5 mL and the following inactive ingredients: sucrose, NF; citric acid, USP; sodium citrate, USP; sodium benzoate, NF; xanthan gum, NF; guar gum, NF; artificial strawberry and cream flavors; silicon dioxide, NF; and magnesium stearate, NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Drug Metabolism

Absorption:

Oral Bioavailability: Maximal plasma cefdinir concentrations occur 2 to 4 hours postdose following capsule or suspension administration. Plasma cefdinir concentrations increase with dose, but the increases are less than dose-proportional from 300 mg (7 mg/kg) to 600 mg (14 mg/kg). Following administration of suspension to healthy adults, cefdinir bioavailability is 120% relative to capsules. Estimated bioavailability of cefdinir capsules is 21% following administration of a 300 mg capsule dose, and 16% following administration of a 600 mg capsule dose. Estimated absolute bioavailability of cefdinir suspension is 25%.

Effect of Food: Although the rate (C_{max}) and extent (AUC) of cefdinir absorption from the capsules are reduced by 16% and 10%, respectively, when given with a high-fat meal, the magnitude of these reductions is not likely to be clinically significant. Therefore, cefdinir may be taken without regard to food.

Cefdinir Capsules: Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 300- and 600-mg oral doses of cefdinir to adult subjects are presented in the following table:

Mean (±SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Capsules to Adult Subjects

Dose	C_{max} (μg/mL)	t_{max} (hr)	AUC (μg·hr/mL)
300 mg	1.60	2.9	7.05
	(0.55)	(0.89)	(2.17)
600 mg	2.87	3.0	11.1
	(1.01)	(0.66)	(3.87)

Cefdinir Suspension: Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 7- and 14-mg/kg oral doses of cefdinir to pediatric subjects (age 6 months–12 years) are presented in the following table:

Mean (±SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Suspension to Pediatric Subjects

Dose	C_{max} (μg/mL)	t_{max} (hr)	AUC (μg·hr/mL)
7 mg/kg	2.30	2.2	8.31
	(0.65)	(0.6)	(2.50)
14 mg/kg	3.86	1.8	13.4
	(0.62)	(0.4)	(2.64)

Omnicef® (Cefdinir) Capsules
Omnicef® (Cefdinir) for Oral Suspension

For organisms other than *Haemophilus* spp. and *Streptococcus* spp:

MIC (μg/mL)	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

For *Haemophilus* spp:[a]

MIC (μg/mL)	Interpretation[b]
≤1	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM).[1]

[b] The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp:

Streptococcus pneumoniae that are susceptible to penicillin (MIC ≤0.06 μg/mL), or streptococci other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤0.12 μg/mL), can be considered susceptible to cefdinir. Testing of cefdinir against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for cefdinir are not available.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures. Standard cefdinir powder should provide the following MIC values:

Microorganism	MIC Range (μg/mL)
Escherichia coli ATCC 25922	0.12-0.5
Haemophilus influenzae ATCC 49766[c]	0.12-0.5
Staphylococcus aureus ATCC 29213	0.12-0.5

[c] This quality control range is applicable only to *H. influenzae* ATCC 49766 tested by a broth microdilution procedure using HTM.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-μg cefdinir to test the susceptibility of microorganisms to cefdinir.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg cefdinir disk should be interpreted according to the following criteria:

For organisms other than *Haemophilus* spp. and *Streptococcus* spp:[d]

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

[d] Because certain strains of *Citrobacter, Providencia,* and *Enterobacter* spp. have been reported to give false susceptible results with the cefdinir disk, strains of these genera should not be tested and reported with this disk.

For *Haemophilus* spp:[e]

Zone Diameter (mm)	Interpretation[f]
≥20	Susceptible

[e] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM.[2]

[f] The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp:

Isolates of *Streptococcus pneumoniae* should be tested against a 1-μg oxacillin disk. Isolates with oxacillin zone sizes ≥20 mm are susceptible to penicillin and can be considered susceptible to cefdinir. Streptococci other than *S. pneumoniae* should be tested with a 10-unit penicillin disk. Isolates with penicillin zone sizes ≥28 mm are susceptible to penicillin and can be considered susceptible to cefdinir.

Multiple Dosing: Cefdinir does not accumulate in plasma following once- or twice-daily administration to subjects with normal renal function.

Distribution: The mean volume of distribution (Vd_{area}) of cefdinir in adult subjects is 0.35 L/kg (±0.29); in pediatric subjects (age 6 months–12 years), cefdinir Vd_{area} is 0.67 L/kg (±0.38). Cefdinir is 60% to 70% bound to plasma proteins in both adult and pediatric subjects; binding is independent of concentration.

Skin Blister: In adult subjects, median (range) maximal blister fluid cefdinir concentrations of 0.65 (0.33-1.1) and 1.1 (0.49-1.9) µg/mL were observed 4 to 5 hours following administration of 300- and 600-mg doses, respectively. Mean (±SD) blister C_{max} and AUC (0-∞) values were 48% (±13) and 91% (±18) of corresponding plasma values.

Tonsil Tissue: In adult patients undergoing elective tonsillectomy, respective median tonsil tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.25 (0.22-0.46) and 0.36 (0.22-0.80) µg/g. Mean tonsil tissue concentrations were 24% (±8) of corresponding plasma concentrations.

Sinus Tissue: In adult patients undergoing elective maxillary and ethmoid sinus surgery, respective median sinus tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were <0.12 (<0.12-0.46) and 0.21 (<0.12-2.0) µg/g. Mean sinus tissue concentrations were 16% (±20) of corresponding plasma concentrations.

Lung Tissue: In adult patients undergoing diagnostic bronchoscopy, respective median bronchial mucosa cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.78 (<0.06-1.33) and 1.14 (<0.06-1.92) µg/mL, and were 31% (±18) of corresponding plasma concentrations. Respective median epithelial lining fluid concentrations were 0.29 (<0.3-4.73) and 0.49 (<0.3-0.59) µg/mL, and were 35% (±83) of corresponding plasma concentrations.

Middle Ear Fluid: In 14 pediatric patients with acute bacterial otitis media, respective median middle ear fluid cefdinir concentrations 3 hours after administration of single 7- and 14-mg/kg doses were 0.21 (<0.09-0.94) and 0.72 (0.14-1.42) µg/mL. Mean middle ear fluid concentrations were 15% (±15) of corresponding plasma concentrations.

CSF: Data on cefdinir penetration into human cerebrospinal fluid are not available.

Metabolism and Excretion: Cefdinir is not appreciably metabolized. Activity is primarily due to parent drug. Cefdinir is eliminated principally via renal excretion with a mean plasma elimination half-life ($t_{1/2}$) of 1.7 (±0.6) hours. In healthy subjects with normal renal function, renal clearance is 2.0 (±1.0) mL/min/kg, and apparent oral clearance is 11.6 (±6.0) and 15.5 (±5.4) mL/min/kg following doses of 300- and 600-mg, respectively. Mean percent of dose recovered unchanged in the urine following 300- and 600-mg doses is 18.4% (±6.4) and 11.6% (±4.6), respectively. Cefdinir clearance is reduced in patients with renal dysfunction (see **Special Populations:** *Patients with Renal Insufficiency*).

Because renal excretion is the predominant pathway of elimination, dosage should be adjusted in patients with markedly compromised renal function or who are undergoing hemodialysis (see **DOSAGE AND ADMINISTRATION**).

Special Populations:

Patients with Renal Insufficiency: Cefdinir pharmacokinetics were investigated in 21 adult subjects with varying degrees of renal function. Decreases in cefdinir elimination rate, apparent oral clearance (CL/F), and renal clearance were approximately proportional to the reduction in creatinine clearance (CL_{cr}). As a result, plasma cefdinir concentrations were higher and persisted longer in subjects with renal impairment than in those without renal impairment. In subjects with CL_{cr} between 30 and 60 mL/min, C_{max} and $t_{1/2}$ increased by approximately 2-fold and AUC by approximately 3-fold. In subjects with CL_{cr} <30 mL/min, C_{max} increased by approximately 2-fold, $t_{1/2}$ by approximately 5-fold, and AUC by approximately 6-fold. Dosage adjustment is recommended in patients with markedly compromised renal function (creatinine clearance <30 mL/min; see **DOSAGE AND ADMINISTRATION**).

Hemodialysis: Cefdinir pharmacokinetics were studied in 8 adult subjects undergoing hemodialysis. Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced apparent elimination $t_{1/2}$ from 16 (±3.5) to 3.2 (±1.2) hours. Dosage adjustment is recommended in this patient population (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: Because cefdinir is predominantly renally eliminated and not appreciably metabolized, studies in patients with hepatic impairment were not conducted. It is not expected that dosage adjustment will be required in this population.

Geriatric Patients: The effect of age on cefdinir pharmacokinetics after a single 300-mg dose was evaluated in 32 subjects 19 to 91 years of age. Systemic exposure to cefdinir was substantially increased in older subjects (N=16). C_{max} by 44% and AUC by 86%. This increase was due to a reduction in cefdinir clearance. The apparent volume of distribution was also reduced, thus no appreciable alterations in apparent elimination half-life were observed (elderly: 2.2 ± 0.6 hours vs young: 1.8 ± 0.4 hours). Since cefdinir clearance has been shown to be primarily related to changes in renal function rather than age, elderly patients do not require dosage adjustment unless they have markedly compromised renal function (creatinine clearance <30 mL/min, see *Patients with Renal Insufficiency*, above).

Gender and Race: The results of a meta-analysis of clinical pharmacokinetics (N=217) indicated no significant impact of either gender or race on cefdinir pharmacokinetics.

Microbiology

As with other cephalosporins, bactericidal activity of cefdinir results from inhibition of cell wall synthesis. Cefdinir is stable in the presence of some, but not all, β-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

Cefdinir has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE**.

Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (including β-lactamase producing strains)
NOTE: Cefdinir is inactive against methicillin-resistant staphylococci.
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms:

Haemophilus influenzae (including β-lactamase producing strains)
Haemophilus parainfluenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefdinir exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefdinir in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:

Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
Viridans group streptococci

NOTE: Cefdinir is inactive against *Enterococcus* and methicillin-resistant *Staphylococcus* species.

Aerobic Gram-Negative Microorganisms:

Citrobacter diversus
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

NOTE: Cefdinir is inactive against *Pseudomonas* and *Enterobacter* species.

Susceptibility Tests:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefdinir powder. The MIC values should be interpreted according to the following criteria:

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefdinir.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures. For the diffusion technique, the 5-µg cefdinir disk should provide the following zone diameters in these laboratory quality control strains:

Organism	Zone Diameter (mm)
Escherichia coli ATCC 25922	24-28
Haemophilus influenzae ATCC 49766[a]	24-31
Staphylococcus aureus ATCC 25923	25-32

[a] This quality control range is applicable only to testing of *H. influenzae* ATCC 49766 using HTM.

INDICATIONS AND USAGE

OMNICEF (cefdinir) Capsules and OMNICEF (cefdinir) for Oral Suspension are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Adults and Adolescents

Community-Acquired Pneumonia caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains) (see **CLINICAL STUDIES**).

Acute Exacerbations of Chronic Bronchitis caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Acute Maxillary Sinusitis caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

NOTE: For information on use in pediatric patients, See **Pediatric Use** and **DOSAGE AND ADMINISTRATION**.

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes* (see **CLINICAL STUDIES**).

NOTE: Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*.

Pediatric Patients

Acute Bacterial Otitis Media caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes* (see **CLINICAL STUDIES**).

NOTE: Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*.

CONTRAINDICATIONS

OMNICEF (cefdinir) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH OMNICEF (CEFDINIR) IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFDINIR, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFDINIR IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFDINIR OCCURS, THE DRUG SHOULD BE DISCONTINUED. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild-to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

PRECAUTIONS

General

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered.

Cefdinir, as with other broad-spectrum antimicrobials (antibiotics), should be prescribed with caution in individuals with a history of colitis.

In patients with transient or persistent renal insufficiency (creatinine clearance <30 mL/min), the total daily dose of OMNICEF should be reduced because high and prolonged plasma concentrations of cefdinir can result following recommended doses (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Antacids containing magnesium or aluminum interfere with the absorption of cefdinir. If this type of antacid is required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Iron supplements, including multivitamins that contain iron, interfere with the absorption of cefdinir. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement.

Iron-fortified infant formula does not significantly interfere with the absorption of cefdinir. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

If the patient is diabetic, he/she/the guardian should be aware that the oral suspension contains 2.86 g of sucrose per teaspoon.

Drug Interactions

Antacids: (aluminum- or magnesium-containing): Concomitant administration of 300-mg cefdinir capsules with 30 mL Maalox® TC suspension reduces rate (C_{max}) and extent (AUC) of absorption by approximately 40%. Time to reach C_{max} is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Probenecid: As with other β-lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak cefdinir

FOR POSITION ONLY

tion.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir suspension in multiple-dose clinical trials (N=1387 cefdinir-treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N = 1387)[a]

Incidence ≥ 1%	Diarrhea	8%
	Rash	3%
	Cutaneous moniliasis	1%
	Vomiting	1%
Incidence <1% but >0.1%	Abdominal pain	0.9%
	Leukopenia[b]	0.4%
	Nausea	0.3%
	Vaginal moniliasis	0.3% of girls
	Vaginitis	0.3% of girls
	Dyspepsia	0.2%
	Maculopapular rash	0.2%
	Increased AST[b]	0.2%

[a] 743 males, 644 females

[b] Laboratory changes were occasionally reported as adverse events.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

LABORATORY VALUE CHANGES OBSERVED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N = 1387)

Incidence ≥1%	↑Lactate dehydrogenase	2%
	↑Alkaline phosphatase	1%
	↓Bicarbonate	1%
	↑Eosinophils	1%
	↑Urine pH	1%
Incidence <1% but >0.1%	↑Lymphocytes, ↓Lymphocytes	0.9, 0.7
	↑Phosphorus, ↓Phosphorus	0.9, 0.4
	↓White blood cells, ↑White blood cells	0.9, 0.4
	↑Urine protein	0.9
	↑PMNs	0.8
	↑Platelets	0.7
	↓Calcium	0.5
	↑AST	0.2
	↓Hemoglobin	0.4
	↑Potassium	0.3
	↑ALT	0.2
	↓Hematocrit	0.2
	↑Urine specific gravity	0.2
	↑Urine white blood cells	0.2

Postmarketing Experience

The following adverse experiences and altered laboratory tests, regardless of their relationship to cefdinir, have been reported during extensive postmarketing experience, beginning with approval in Japan in 1991: Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, erythema nodosum, conjunctivitis, stomatitis, acute hepatitis, cholestasis, fulminant hepatitis, hepatic failure, jaundice, increased amylase, shock, anaphylaxis, facial and laryngeal edema, feeling of suffocation, acute enterocolitis, bloody diarrhea, hemorrhagic colitis, melena, pseudomembranous colitis, pancytopenia, granulocytopenia, leukopenia, thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, acute respiratory failure, asthmatic attack, drug-induced pneumonia, eosinophilic pneumonia, idiopathic interstitial pneumonia, fever, acute renal failure, nephropathy, bleeding tendency, coagulation disorder, disseminated intravascular coagulation, upper GI bleed, peptic ulcer, ileus, loss of consciousness, allergic vasculitis, possible cefdinir-diclofenac interaction, cardiac failure, chest pain, myocardial infarction, hypertension, involuntary movements, and rhabdomyolysis.

Cephalosporin Class Adverse Events

The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics in general:

Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment (see **WARNINGS**).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

Information on cefdinir overdosage in humans is not available. In acute rodent toxicity studies, a single oral 5600-mg/kg dose produced no adverse effects. Toxic signs and symptoms following overdosage with other β-lactam antibiotics have included nausea, vomiting, epigastric distress, diarrhea, and convulsions. Hemodialysis removes cefdinir from the body. This may be useful in the event of a serious toxic reaction from over-

European Community-Acquired Pneumonia Study
Cefdinir vs Amoxicillin/Clavulanate

	Cefdinir BID	Amoxicillin/ Clavulanate TID	Outcome
Clinical Cure Rates	83/104 (80%)	86/97 (89%)	Cefdinir not equivalent to control
Eradication Rates			
Overall	85/96 (89%)	84/90 (93%)	Cefdinir equivalent to control
S. pneumoniae	42/44 (95%)	43/44 (98%)	
H. influenzae	26/35 (74%)	21/26 (81%)	
M. catarrhalis	6/6 (100%)	8/8 (100%)	
H. parainfluenzae	11/11 (100%)	12/12 (100%)	

Streptococcal Pharyngitis/Tonsillitis

In four controlled studies conducted in the United States, cefdinir was compared with 10 days of penicillin in adults, adolescents, and pediatric patients. Two studies (one in adults and adolescents, the other in pediatric patients) compared 10 days of cefdinir QD or BID to penicillin 250 mg or 10 mg/kg QID. Using strict evaluability and microbiologic/clinical response criteria 5 to 10 days posttherapy, the following clinical cure rates, microbiologic eradication rates, and statistical outcomes were obtained (see table below):

Pharyngitis/Tonsillitis Studies
Cefdinir (10 days) vs Penicillin (10 days)

Study	Efficacy Parameter	Cefdinir QD	Cefdinir BID	Penicillin QID	Outcome
Adults/ Adolescents	Eradication of *S. pyogenes*	192/210 (91%)	199/217 (92%)	181/217 (83%)	Cefdinir superior to control
	Clinical Cure Rates	199/210 (95%)	209/217 (96%)	193/217 (89%)	Cefdinir superior to control
Pediatric Patients	Eradication of *S. pyogenes*	215/228 (94%)	214/227 (94%)	159/227 (70%)	Cefdinir superior to control
	Clinical Cure Rates	222/228 (97%)	218/227 (96%)	196/227 (86%)	Cefdinir superior to control

Two studies (one in adults and adolescents, the other in pediatric patients) compared 5 days of cefdinir BID to 10 days of penicillin 250 mg or 10 mg/kg QID. Using strict evaluability and microbiologic/clinical response criteria 4 to 10 days posttherapy, the following clinical cure rates, microbiologic eradication rates, and statistical outcomes were obtained (see table below):

Pharyngitis/Tonsillitis Studies
Cefdinir (5 days) vs Penicillin (10 days)

Study	Efficacy Parameter	Cefdinir BID	Penicillin QID	Outcome
Adults/ Adolescents	Eradication of *S. pyogenes*	193/218 (89%)	176/214 (82%)	Cefdinir equivalent to control
	Clinical Cure Rates	194/218 (89%)	181/214 (85%)	Cefdinir equivalent to control
Pediatric Patients	Eradication of *S. pyogenes*	176/196 (90%)	135/193 (70%)	Cefdinir superior to control
	Clinical Cure Rates	179/196 (91%)	173/193 (90%)	Cefdinir equivalent to control

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 4th ed. Approved Standard, NCCLS Document M7-A4, Vol 17(2). NCCLS, Villanova, PA, Jan 1997.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests, 6th ed. Approved Standards, NCCLS Document M2-A6, Vol 17(1). NCCLS, Villanova, PA, Jan 1997.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron, 1976;16:31-41.
4. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259-63.
5. Schwartz GJ, Feld LG, Langford DJ. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. J Pediatrics 1984;104:849-54.

Caution: Federal law prohibits dispensing without prescription.

January 1998

Manufactured by:
Lilly del Caribe, Inc.
Carolina, Puerto Rico 00986
For:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

0067G050

plasma levels, and a 50% prolongation in the apparent elimination half-life.

Iron Supplements and Foods Fortified With Iron: Concomitant administration of cefdinir with a therapeutic iron supplement containing 60 mg of elemental iron (as $FeSO_4$) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement.

The effect of foods highly fortified with elemental iron (primarily iron-fortified breakfast cereals) on cefdinir absorption has not been studied.

Concomitantly administered iron-fortified infant formula (2.2 mg elemental iron/6 oz) has no significant effect on cefdinir pharmacokinetics. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

There have been rare reports of reddish stools in patients who have received cefdinir in Japan. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide. The administration of cefdinir may result in a false-positive reaction for glucose in urine using Clinitest®, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used. Cephalosporins are known to occasionally induce a positive direct Coombs' test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cefdinir has not been evaluated. No mutagenic effects were seen in the bacterial reverse mutation assay (Ames) or point mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus (HGPRT) in V79 Chinese hamster lung cells. No clastogenic effects were observed *in vitro* in the structural chromosome aberration assay in V79 Chinese hamster lung cells or *in vivo* in the micronucleus assay in mouse bone marrow. In rats, fertility and reproductive performance were not affected by cefdinir at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m^2/day).

Pregnancy - Teratogenic Effects

Pregnancy Category B: Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m^2/day) or in rabbits at oral doses up to 10 mg/kg/day (0.7 times the human dose based on mg/kg/day, 0.23 times based on mg/m^2/day). Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased body weight occurred in rat fetuses at ≥100 mg/kg/day, and in rat offspring at ≥32 mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Cefdinir has not been studied for use during labor and delivery.

Nursing Mothers

Following administration of single 600-mg doses, cefdinir was not detected in human breast milk.

Pediatric Use

Safety and efficacy in neonates and infants less than 6 months of age have not been established. Use of cefdinir for the treatment of acute maxillary sinusitis in pediatric patients (age 6 months through 12 years) is supported by evidence from adequate and well-controlled studies in adults and adolescents, the similar pathophysiology of acute sinusitis in adult and pediatric patients, and comparative pharmacokinetic data in the pediatric population.

Geriatric Use

Efficacy is comparable in geriatric patients and younger adults. While cefdinir has been well-tolerated in all age groups, in clinical trials geriatric patients experienced a lower rate of adverse events, including diarrhea, than younger adults. Dose adjustment in elderly patients is not necessary unless renal function is markedly compromised (see **DOSAGE AND ADMINISTRATION**).

ADVERSE EVENTS

Clinical Trials - OMNICEF Capsules (Adult and Adolescent Patients):

In clinical trials, 4527 adult and adolescent patients (3275 US and 1252 non-US) were treated with the recommended dose of cefdinir capsules (600 mg/day). Most adverse events were mild and self-limiting in nature. No deaths or permanent disabilities were attributed to cefdinir. One hundred twenty-five of 4527 (3%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or nausea. Seventeen of 4527 (0.4%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by the investigators to be possibly, probably, or definitely related to cefdinir capsules in multiple-dose clinical trials (N = 3275 cefdinir-treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3275)[a]

Incidence ≥1%	Diarrhea	16%
	Vaginal moniliasis	5% of women
	Nausea	3%
	Headache	2%
	Abdominal pain	1%
	Vaginitis	1% of women
Incidence <1% but >0.1%	Rash	0.9%
	Dyspepsia	0.8%
	Flatulence	0.6%
	Vomiting	0.6%
	Anorexia	0.3%
	Constipation	0.3%
	Abnormal stools	0.2%
	Asthenia	0.2%
	Dizziness	0.2%
	Insomnia	0.2%
	Leukorrhea	0.2% of women
	Pruritus	0.2%
	Somnolence	0.2%

[a] 1469 males, 1806 females

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

LABORATORY VALUE CHANGES OBSERVED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N = 3275)

Incidence ≥ 1%	↑Gamma-glutamyltransferase	1%
	↑Urine protein	1%
	↑Urine red blood cells	1%
Incidence <1% but >0.1%	↑Glucose, ↓ Glucose	0.9, 0.2
	↑Alanine aminotransferase (ALT)	0.9
	↑Urine glucose	0.9
	↑White blood cells, ↓White blood cells	0.8, 0.7
	↓Lymphocytes, ↑Lymphocytes	0.8, 0.2
	↑Urine specific gravity	0.8
	↓Bicarbonate	0.6
	↑Eosinophils	0.6
	↑Phosphorus, ↓Phosphorus	0.6, 0.3
	↑Aspartate aminotransferase (AST)	0.4
	↑Urine white blood cells	0.4
	↓Hemoglobin	0.3
	↑Alkaline phosphatase	0.2
	↑Blood urea nitrogen (BUN)	0.2
	↑Bilirubin	0.2
	↑Lactate dehydrogenase	0.2
	↑Platelets	0.2
	↓Polymorphonuclear neutrophils (PMNs)	0.2
	↑Potassium	0.2
	↑Urine pH	0.2

Clinical Trials - OMNICEF for Oral Suspension (Pediatric Patients):

In clinical trials, 1893 pediatric patients (1387 US and 506 non-US) were treated with the recommended dose of cefdinir suspension (14 mg/kg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. Thirty-nine of 1893 (2%) patients discontinued medication due to adverse events considered by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. Discontinuations were primarily for gastrointestinal disturbances, usually diarrhea. Five of 1893 (0.3%) patients were discontinued due to rash thought related to cefdinir administration.

Omnicef® (Cefdinir) Capsules
Omnicef® (Cefdinir) for Oral Suspension

dosage, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION
(see **INDICATIONS AND USAGE** for Indicated Pathogens)

Capsules

The recommended dosage and duration of treatment for infections in adults and adolescents are described in the following chart; the total daily dose for all infections is 600 mg. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in pneumonia or skin infections; therefore, OMNICEF Capsules should be administered twice daily in these infections. OMNICEF Capsules may be taken without regard to meals.

Adults and Adolescents (Age 13 Years and Older)

Type of Infection	Dosage	Duration
Community-Acquired Pneumonia	300 mg q12h	10 days
Acute Exacerbations of Chronic Bronchitis	300 mg q12h	10 days
	or	
	600 mg q24h	10 days
Acute Maxillary Sinusitis	300 mg q12h	10 days
	or	
	600 mg q24h	10 days
Pharyngitis/Tonsillitis	300 mg q12h	5 to 10 days
	or	
	600 mg q24h	10 days
Uncomplicated Skin and Skin Structure Infections	300 mg q12h	10 days

Powder for Oral Suspension

The recommended dosage and duration of treatment for infections in pediatric patients are described in the following chart; the total daily dose for all infections is 14 mg/kg, up to a maximum dose of 600 mg per day. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in skin infections; therefore, OMNICEF for Oral Suspension should be administered twice daily in this infection. OMNICEF for Oral Suspension may be administered without regard to meals.

Pediatric Patients (Age 6 Months Through 12 Years)

Type of Infection	Dosage	Duration
Acute Bacterial Otitis Media	7 mg/kg q12h	10 days
	or	
	14 mg/kg q24h	10 days
Acute Maxillary Sinusitis	7 mg/kg q12h	10 days
	or	
	14 mg/kg q24h	10 days
Pharyngitis/Tonsillitis	7 mg/kg q12h	5 to 10 days
	or	
	14 mg/kg q24h	10 days
Uncomplicated Skin and Skin Structure Infections	7 mg/kg q12h	10 days

OMNICEF FOR ORAL SUSPENSION PEDIATRIC DOSAGE CHART

Weight	125 mg/5 mL
9 kg/20 lbs	2.5 mL (½ tsp) q12h or 5 mL (1 tsp) q24h
18 kg/40 lbs	5 mL (1 tsp) q12h or 10 mL (2 tsp) q24h
27 kg/60 lbs	7.5 mL (1½ tsp) q12h or 15 mL (3 tsp) q24h
36 kg/80 lbs	10 mL (2 tsp) q12h or 20 mL (4 tsp) q24h
≥ 43 kg[a]/95 lbs	12 mL (2½ tsp) q12h or 24 mL (5 tsp) q24h

[a] Pediatric patients who weigh ≥43 kg should receive the maximum daily dose of 600 mg.

Patients With Renal Insufficiency

For adult patients with creatinine clearance <30 mL/min, the dose of cefdinir should be 300 mg given once daily.

Creatinine clearance is difficult to measure in outpatients. However, the following formula may be used to estimate creatinine clearance (CL_{cr}) in adult patients. For estimates to be valid, serum creatinine levels should reflect steady-state levels of renal function.

Males: $$CL_{cr} = \frac{(\text{weight})\ (140 - \text{age})}{(72)\ (\text{serum creatinine})}$$

Females: $CL_{cr} = 0.85 \times$ above value

where creatinine clearance is in mL/min, age is in years, weight is in kilograms, and serum creatinine is in mg/dL.[3]

The following formula may be used to estimate creatinine clearance in pediatric patients:

$$CL_{cr} = K \times \frac{\text{body length or height}}{\text{serum creatinine}}$$

where K=0.55 for pediatric patients older than 1 year[4] and 0.45 for infants (up to 1 year)[5].

In the above equation, creatinine clearance is in mL/min/1.73 m^2, body length or height is in centimeters, and serum creatinine is in mg/dL.

For pediatric patients with a creatinine clearance of <30 mL/min/1.73 m^2, the dose of cefdinir should be 7 mg/kg (up to 300 mg) given once daily.

Patients on Hemodialysis

Hemodialysis removes cefdinir from the body. In patients maintained on chronic hemodialysis, the recommended initial dosage regimen is a 300-mg or 7-mg/kg dose every other day. At the conclusion of each hemodialysis session, 300 mg (or 7 mg/kg) should be given. Subsequent doses (300 mg or 7 mg/kg) are then administered every other day.

Directions for Mixing OMNICEF for Oral Suspension

Final Concentration	Final Volume (mL)	Amount of Water	Directions
125 mg/5 mL	60	39 mL	Tap bottle to loosen powder, then add water in 2 portions. Shake well after each aliquot.
	100	65 mL	

After mixing, the suspension can be stored at room temperature (25°C/77°F). The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be used for 10 days, after which any unused portion must be discarded.

HOW SUPPLIED

OMNICEF Capsules, containing 300 mg cefdinir, as lavender and turquoise capsules imprinted with the product name, are available as follows:

60 Capsules/Bottle N 0071-0067-20

OMNICEF for Oral Suspension is a cream-colored powder formulation that, when reconstituted as directed, contains 125 mg cefdinir/5 mL. The reconstituted suspension has a cream color and strawberry flavor. The powder is available as follows:

60-mL bottles N 0071-2006-16

100-mL bottles N 0071-2006-18

Store the capsules and unsuspended powder at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Once reconstituted, the oral suspension can be stored at controlled room temperature for 10 days.

CLINICAL STUDIES

Community-Acquired Bacterial Pneumonia

In a controlled, double-blind study in adults and adolescents conducted in the US, cefdinir BID was compared with cefaclor 500 mg TID. Using strict evaluability and microbiologic/clinical response criteria 6 to 14 days posttherapy, the following clinical cure rates, presumptive microbiologic eradication rates, and statistical outcomes were obtained (see table below):

US Community-Acquired Pneumonia Study
Cefdinir vs Cefaclor

	Cefdinir BID	Cefaclor TID	Outcome
Clinical Cure Rates	150/187 (80%)	147/186 (79%)	Cefdinir equivalent to control
Eradication Rates			
Overall	177/195 (91%)	184/200 (92%)	Cefdinir equivalent to control
S. pneumoniae	31/31 (100%)	35/35 (100%)	
H. influenzae	55/65 (85%)	60/72 (83%)	
M. catarrhalis	10/10 (100%)	11/11 (100%)	
H. parainfluenzae	81/89 (91%)	78/82 (95%)	

In a second controlled, investigator-blind study in adults and adolescents conducted primarily in Europe, cefdinir BID was compared with amoxicillin/clavulanate 500/125 mg TID. Using strict evaluability and clinical response criteria 6 to 14 days posttherapy, the following clinical cure rates, presumptive microbiologic eradication rates, and statistical outcomes were obtained (see table below):

EXHIBIT 3

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-739
NDA 50-749

Parke-Davis
Attention: Drusilla Scott, Ph.D.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

Dear Dr. Scott:

Please refer to your new drug applications dated September 3, 1996 (NDA 50-739) and December 30, 1996 (NDA 50-749), received September 4, 1996 and December 31, 1996 respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omnicef (cefdinir) Capsules and Powder for Oral Suspension. We note that these products are subject to the exception provisions of Section 125 (2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated September 24, November 13, December 16, and December 31, 1996; and January 31, February 21, March 10, March 31, April 25, May 6, May 9, June 2, June 11, June 23, June 30, July 1, July 7, July 8, July 9, July 21, July 22, August 8, August 14, August 27, August 29, September 10, September 18, September 29, October 7, October 16, October 20, October 27, November 7, November 18, November 25, and December 3, 1997. The original User Fee goal date for these applications was September 4, 1997 (NDA 50-739) and December 31, 1997 (NDA 50-749). Your submission of June 23, 1997 extended the User Fee goal date for NDA 50-739 to December 4, 1997.

These new drug applications provide for treatment of patients with community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.

We have completed the review of these applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the products with FPL that is not identical to this draft labeling may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL

PRINTED LABELING" for approved NDA's 50-739, 50-749. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated October 20 and December 3, 1997. These commitments, along with any completion dates agreed upon, are listed below.

1. Adherence to regulatory specifications for the drug substance, regulatory specifications for the individual impurities in the cefdinir drug substance, regulatory specifications for the cefdinir 300 mg capsules, regulatory specifications for impurities, shelf-life, and stability commitments for the first three (3) production batches and annual batches as outlined in *CMC Attachment #1*.

2. Submission of the stability data for the first three (3) production batches of the capsules, when available.

3. Submission of dissolution profile results from 10 to 45 minutes for the three (3) NDA pilot batches of powder for oral suspension (lots D40115, D40116, and D40117) at 15 and 18 months. The dissolution test results (single point at 30 minutes) for commercial batches will be reported in the annual reports.

4. As per the GMP audit, the field office has recommended a 4% overage for the powder for oral suspension based on the audited data. The formal validation studies will have to justify any additional overage. Additional overage can be justified on the basis of validation data which should include in-process assays at all critical steps to account for the total manufacturing losses.

5. The pre-NDA lots TSK 04597, TSK 03897, and TSK 03797 can be used for supporting stability data by including testing which was not performed in the NDA batches. However, these batches can not be used for the post-approval commitment batches since these batches contain 7% overage.

6. Adherence to regulatory specifications for the cefdinir powder for oral suspension, regulatory specifications for related substances in the cefdinir powder for oral suspension, shelf-life, and the stability protocols as outlined in

CMC Attachment #2.

7. Submission of the stability data for the first three (3) productions batches of the powder for oral suspension, when available.

Protocols, data, and final reports should be submitted to your IND for these products and a copy of the cover letters sent to these NDA's. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to these NDA's as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to these applications, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2120.

Sincerely yours,

David Feigal, M.D., M.P.H.
Acting Office Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURES

EXHIBIT 4

PATENT

United States Patent [19]

Takaya et al.

[11] **Patent Number: 4,559,334**

[45] **Date of Patent: Dec. 17, 1985**

[54] **7-SUBSTITUTED-3-VINYL-3-CEPHEM COMPOUNDS AND PROCESSES FOR PRODUCTION OF THE SAME**

[75] Inventors: **Takao Takaya, Kawanishi; Hisashi Takasugi, Osaka; Takashi Masugi, Ikeda; Hideaki Yamanaka, Hirakata; Kohji Kawabata, Osaka, all of Japan**

[73] Assignee: **Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan**

[21] Appl. No.: **543,880**

[22] Filed: **Oct. 20, 1983**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 428,970, Sep. 30, 1982, abandoned, which is a continuation-in-part of Ser. No. 205,334, Nov. 10, 1980, Pat. No. 4,409,214.

[30] **Foreign Application Priority Data**

Aug. 26, 1983 [GB] United Kingdom 8323034

[51] **Int. Cl.**[4] C07D 501/24; A61K 31/545

[52] **U.S. Cl.** 514/202; 544/22; 544/23

[58] **Field of Search** 544/22, 23; 424/246; 514/202

[56] **References Cited**

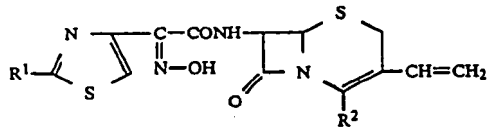
U.S. PATENT DOCUMENTS

3,994,884	11/1976	Weir	544/22
4,107,431	8/1978	Clark et al.	544/16
4,264,595	4/1981	Numata et al.	544/22

Primary Examiner—Donald G. Daus
Assistant Examiner—Robert Benson
Attorney, Agent, or Firm—Oblon, Fisher, Spivak, McClelland & Maier

[57] **ABSTRACT**

The invention relates to novel compounds of high antimicrobial activity of the formula:



in which

R^1 is amino or a protected amino group, and

R^2 is carboxy or a protected carboxy group, and a pharmaceutically acceptable salt thereof.

20 Claims, No Drawings

7-SUBSTITUTED-3-VINYL-3-CEPHEM COMPOUNDS AND PROCESSES FOR PRODUCTION OF THE SAME

This application is a continuation-in-part of application Ser. No. 428,970, filed Sept. 30, 1982 now abandoned, which in turn is a continuation-in-part of application Ser. No. 205,334, filed Nov. 10, 1980, now U.S. Pat. No. 4,409,214.

The present invention relates to novel 7-substituted-3-vinyl-3-cephem compounds and a pharmaceutically acceptable salt thereof.

More particularly, it relates to novel 7-substituted-3-vinyl-3-cephem compounds and a pharmaceutically acceptable salt thereof, which have antimicrobial activity, to processes for the production of the same, to a pharmacetical composition comprising the same, and to a method for the treatment of infectious diseases caused by pathogenic microorganisms comprising administering the same to infected human being or animals.

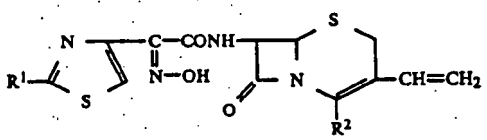
Accordingly, one object of the present invention is to provide novel 7-substituted-3-vinyl-3-cephem compounds and a pharmaceutically acceptable salt thereof, which are highly active against a number of pathogenic microorganisms and are useful as antimicrobial agents, especially for oral administration.

Another object of the present invention is to provide processes for the production of novel 7-substituted-3-vinyl-3-cephem compounds and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said 7-substituted-3-vinyl-3-cephem compounds and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a method for the treatment of infectious diseases caused by pathogenic microorganisms which comprises administering said 7-substituted-3-vinyl-3-cephem compounds and a pharmaceutically acceptable salt thereof to the infected human being or animals.

The 7-substituted-3-vinyl-3-cephem compounds according to this invention are novel and can be represented by the following general formula (I).



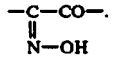
(I)

in which

R^1 is amino or a protected amino group, and

R^2 is carboxy or a protected carboxy group.

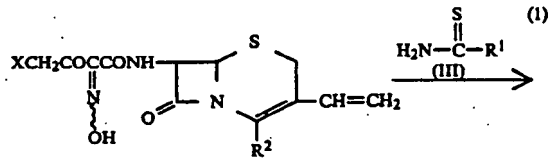
It is to be understood that the term "syn isomer" used in the present specification means the compound (I) having the stereospecific partial structure of the formula:



Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.) etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like.

The object compound (I) or a pharmaceutically acceptable salt thereof of this invention can be produced by the processes illustrated below.

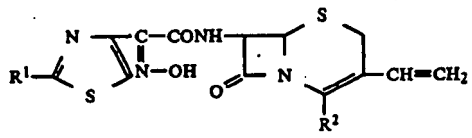
Process 1:



(II)
or a salt thereof

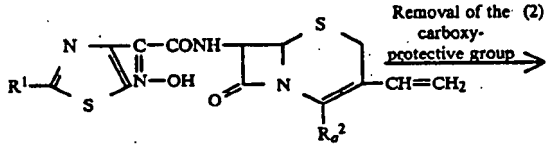
(1)

(III)



(I)
or a salt thereof

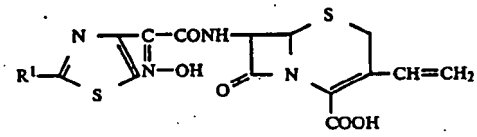
Process 2:



(Ia)
or a salt thereof

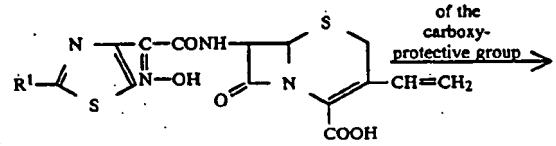
(2)

Removal of the carboxy-protective group



(Ib)
or a salt thereof

Process 3:

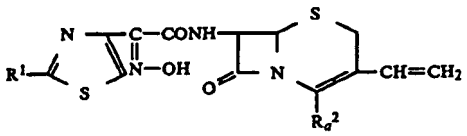


(Ib)
or a reactive derivative at the carboxy group thereof, or a salt thereof

(3)

Introduction of the carboxy-protective group

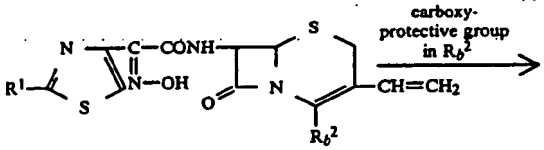
-continued



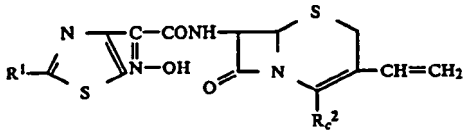
(Ia)
or a salt thereof

Process 4:

Removal of the carboxy-protective group in R_b^2 (4)



(Ic)
or a salt thereof



(Id)
or a salt thereof

in which

R^1 and R^2 are each as defined above,

X is halogen,

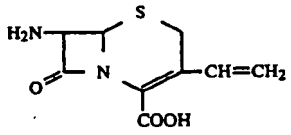
R_a^2 is a protected carboxy group,

R_b^2 is protected carboxy(lower)alkoxycarbonyl, and

R_c^2 is carboxy(lower)alkoxycarbonyl.

With regard to the starting compound (II) used in Process 1, said compound (II) is new and can be prepared, for example, by the following processes.

Process A:



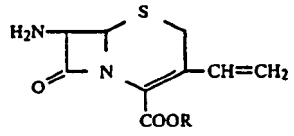
(IVa)

or a reactive derivative at the carboxy group thereof, or a salt thereof

R—OH

or a reactive derivative at the hydroxy group, or a salt thereof

(V)

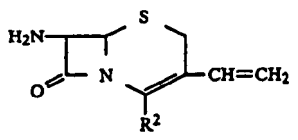


(IV_b)

or a salt thereof

Process B:

-continued



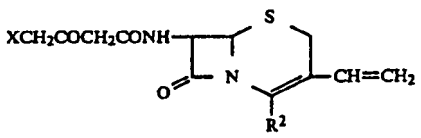
(IV)

or a reactive derivative at the amino group thereof, or a salt thereof

(VI)

1 $X—CH_2COCH_2COOH$

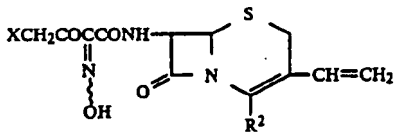
or a reactive derivative at the carboxy group or a salt thereof



(VII)

or a salt thereof

2 Nitrosating Agent



(II)

or a salt thereof

in which

R^2 and X are each as defined above, and

the group "COOR" is a protected carboxy group.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

The term "higher" is intended to mean 7 to 20 carbon atoms, unless otherwise indicated.

Suitable "protected amino" group may include an amino group substituted by a conventional amino-protective group which is used in penicillin and cephalosporin compounds, for example, acyl as mentioned below, ar(lower)alkyl such as mono-(or di or tri)phenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, etc.), lower alkoxycarbonyl(lower)alkylidene or its enamine tautomer (e.g. 1-methoxycarbonyl-1-propen-2-yl, etc.), di(lower)alkylaminomethylene (e.g. dimethylaminomethylene, etc.), etc.

Suitable "acyl" may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic acyl substituted with aromatic or heterocyclic group(s).

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), (C_3–C_7)-cycloalk-

anecarbonyl (e.g. cyclohexanecarbonyl, etc.), amidino, and the like.

The aromatic acyl may include aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.), arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), and the like.

The heterocyclic acyl may include heterocyclecarbonyl (e.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, tetrazolylcarbonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group(s) may include ar(lower)alkanoyl such as phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), ar(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), phenoxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.), and the like.

The aliphatic acyl substituted with heterocyclic group(s) may include thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl, thiadiazolylpropionyl, and the like.

These acyl groups may be further substituted with one or more suitable substituents such as lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.), halogen (e.g. chlorine, bromine, iodine, fluorine), lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.), lower alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, hexylthio, etc.), nitro and the like, and preferable acyl having such substituent(s) may be mono (or di or tri)halo(lower)alkanoyl (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl, etc.), mono (or di or tri)halo(lower)alkoxycarbonyl (e.g. chloromethoxycarbonyl, dichloromethoxycarbonyl, 2,2,2-tri-chloroethoxycarbonyl, etc.), nitro (or halo or lower alkoxy)phenyl(lower)alkoxycarbonyl (e.g. nitrobenzyloxycarbonyl, chlorobenzyloxycarbonyl, methoxybenzyloxycarbonyl, etc.), and the like.

Suitable "protected carboxy" group and "protected carboxy" moiety in the term "protected carboxy(lower)alkoxycarbonyl" may include an esterified carboxy group which is conventionally used in penicillin or cephalosporin compound.

Suitable "ester moiety" in "esterified carboxy group" may include lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.), lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.), lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.), lower alkoxy(lower)alkyl ester (e.g. methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.), lower alkylthio(lower)alkyl ester (e.g. methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropylthiomethyl ester, etc.), carboxy-substituted-lower alkyl ester (e.g. carboxymethyl ester, 2-carboxyethyl ester, 3-carboxypropyl ester, etc.), protected carboxy-substituted-lower alkyl ester such as lower alkoxycarbonyl-substituted-lower alkyl ester (e.g. tert-butoxycarbonylmethyl ester, 2-tert-butoxycarbonylethyl ester, 3-tert-butoxycarbonylpropyl ester, etc.), mono(or di or tri)halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)pentanoyloxyethyl ester, etc.], higher alkanoyloxy(lower)alkyl ester [e.g. heptanoyloxymethyl ester, octanoyloxymethyl ester, nonanoyloxymethyl ester, decanoyloxymethyl ester, undecanoyloxymethyl ester, lauroyloxymethyl ester, tridecanoyloxymethyl ester, myristoyloxymethyl ester, pentadecanoyloxymethyl ester, palmitoyloxymethyl ester, heptadecanoyloxymethyl ester, stearoyloxymethyl ester, nonadecanoyloxymethyl ester, eicosanoyloxymethyl ester, 1(or 2)-heptanoyloxyethyl ester, 1(or 2)-octanoyloxyethyl ester, 1(or 2)-nonanoyloxyethyl ester, 1(or 2)-decanoyloxyethyl ester, 1(or 2)undecanoyloxyethyl ester, 1(or 2)-lauroyloxyethyl ester, 1(or 2)-tridecanoyloxyethyl ester, 1(or 2)-myristoyloxyethyl ester, 1(or 2)-pentadecanoyloxyethyl ester, 1(or 2)palmitoyloxyethyl ester, 1(or 2)-heptadecanoyloxyethyl ester, 1(or 2)-stearoyloxyethyl ester, 1(or 2)-nonadecanoyloxyethyl ester, 1(or 2)-eicosanoyloxyethyl ester, etc.], lower alkoxycarbonyloxy(lower)alkyl ester [e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, isopropoxycarbonyloxymethyl ester, tert-butoxycarbonyloxymethyl ester, 1(or 2)-methoxycarbonyloxyethyl ester, 1(or 2)ethoxycarbonyloxyethyl ester, 1(or 2)-propoxycarbonyloxyethyl ester, 1(or 2)-isopropoxycarbonyloxyethyl ester, 1(or 2)-butoxycarbonyloxyethyl ester, 1(or 2)-isobutoxycarbonyloxyethyl ester, 1(or 2)-tertbutoxycarbonyloxyethyl ester, 1(or 2)-hexyloxycarbonyloxyethyl ester, 1(or 2 or 3)-methoxycarbonyloxypropyl ester, 1(or 2 or 3)-ethoxycarbonyloxypropyl ester, 1(or 2 or 3)-isopropoxycarbonyloxypropyl ester, 1(or 2 or 3 or 4)-ethoxycarbonyloxybutyl ester, 1(or 2 or 3 or 4)butoxycarbonyloxybutyl ester, 1(or 2 or 3 or 4 or 5)pentyloxycarbonyloxypentyl ester, 1 (or 2 or 3 or 4 or 5)neopentyloxycarbonyloxypentyl ester, 1 (or 2 or 3 or 4 or 5 or 6)-ethoxycarbonyloxyhexyl ester, etc.], (5-lower alkyl-2-oxo-1,3-dioxol-4-yl) (lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester (e.g. mesylmethyl ester, 2-mesylethyl ester, etc.), ar(lower)alkyl ester which may have one or more substituent(s) such as mono(or di or tri)phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, benzhydryl ester, trityl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.), aryl ester which may have one or more suitable substituents (e.g. phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, salicyl ester, etc.), heterocyclic ester (e.g. phthalidyl ester, etc.), and the like.

Suitable "halogen" may include chlorine, bromine, iodine, and the like.

Suitable "lower alkoxycarbonyl" group in the terms "protected carboxy(lower)alkoxycarbonyl" and "carboxy(lower)alkoxycarbonyl" may include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, and the like.

Suitable "lower alkoxycarbonyloxy(lower)alkyl" group may include methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, propoxycarbonyloxymethyl, iso-

propoxycarbonyloxymethyl, tert-butoxycarbonyloxymethyl, 1(or 2)methoxycarbonyloxyethyl, 1(or 2)-ethoxycarbonyloxyethyl, 1(or 2)-propoxycarbonyloxyethyl, 1(or 2)-isopropoxycarbonyloxyethyl, 1(or 2)-butoxycarbonyloxyethyl, 1(or 2)-isobutoxycarbonyloxyethyl, 1(or 2)-tertbutoxycarbonyloxyethyl, 1(or 2)-hexyloxycarbonyloxyethyl, 1(or 2 or 3)-methoxycarbonyloxypropyl, 1(or 2 or 3)ethoxycarbonyloxypropyl, 1(or 2 or 3)-isopropoxycarbonyloxypropyl, 1(or 2 or 3 or 4)-ethoxycarbonyloxybutyl, 1(or 2 or 3 or 4)-butoxycarbonyloxybutyl, 1(or 2 or 3 or 4 or 5)-pentyloxycarbonyloxypentyl, 1-(or 2 or 3 or 4 or 5)neopentyloxycarbonyloxypentyl, 1(or 2 or 3 or 4 or 5 or 6)ethoxycarbonyloxyhexyl, and the like.

Preferable embodiments of the object compound (I) are as follows.

Preferable embodiment of R^1 is amino; and R^2 is carboxy or esterified carboxy [more preferably carboxy-substituted-lower alkoxycarbonyl, lower alkoxycarbonyl-substituted-lower alkoxycarbonyl, lower alkanoyloxy(lower)alkoxycarbonyl, higher alkanoyloxy(lower)alkoxycarbonyl, lower alkoxycarbonyloxy(lower)alkoxycarbonyl, (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)-(lower)alkoxycarbonyl, ar(lower)alkoxycarbonyl (e.g., diphenyl(lower)alkoxycarbonyl), or phthalidyloxycarbonyl].

The processes for the production of the compound (I) or a salt thereof will be explained in detail as follows.

(1) Process 1

The compound (I) or a salt thereof can be produced by reacting the compound (II) or a salt thereof with the compound (III).

Suitable salt of the compound (II) may include the same salt with a base as exemplified for the compound (I).

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as ethyl acetate, methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, water, acetic acid, formic acid, etc. or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under cooling to warming.

Process 2

The compound (Ib) or a salt thereof can be produced by subjecting the compound (Ia) or a salt thereof to the removal reaction of the carboxy-protective group.

Suitable salts of the compounds (Ia) and (Ib) may include the same ones as exemplified for the compound (I).

Suitable method for this removal reaction may include conventional one such as hydrolysis, reduction, or the like.

(i) For hydrolysis:

Hydrolysis is preferably carried out in the presence of an acid.

Suitable acid may be an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, propionic acid, methanesulfonic acid, benzenesulfonic acid, p-toluensulfonic acid, etc.), an acidic ion-exchange resin and the like. In case that the organic acid such as trifluoroacetic acid and p-toluenesulfonic acid is used in this reaction, the reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, etc.).

Further, instead of the above acid, Lewis acid such as boron trifluoride, boron trifluoride etherate, alminum trichloride, antimony pentachloride, ferric chloride, stannic chloride, titanium tetrachloride, zinc chloride, and the like can also be used in this reaction, and in case of using Lewis acid, the reaction can preferably be carried out in the presence of cation trapping agent (e.g. anisole).

The hydrolysis is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, tert-butyl alcohol, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane or a mixture thereof, and further the above-mentioned acids can also be used as a solvent when they are in liquid.

The reaction temperature of this hydrolysis is not critical, and the reaction is usually conducted under cooling to at somewhat elevated temperature.

(ii) For Reduction

Reduction is conducted in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like.

The reduction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually conducted under cooling to warming.

Process 3

The compound (Ia) or a salt thereof can be produced by introducing a carboxy-protective group into the compound (Ib) or a reactive derivative at the carboxy group thereof, or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (Ib) may include conventional one which can be applied to this reaction such as acid halide (e.g. acid chloride, acid bromide, etc.), or the like.

The introducing agent of a carboxy-protective group to be used in this reaction may include a conventional esterifying agent such as an alcohol or its reactive

equivalent (e.g. halide, sulfonate, sulfate, diazo compound, etc.), and the like.

The present reaction can also be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoate (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), 1,8-diazabicyclo[5,4,0]undec-7-en, pyridines (e.g. pyridine, lutidine picoline, etc.), quinoline and the like, and can also be carried out in the presence of metal iodide (e.g. sodium iodide, potassium iodide, etc.).

In case that the alcohol is used as the introducing agent of a carboxy-protective group, the reaction can be carried out in the presence of a condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.], a sulfonic acid esterof N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.], or the like.

This reaction is usually conducted in a solvent which does not adversely influence the reaction such as acetone, dioxane, acetonitrile, chloroform, benzene, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, pyridine, hexamethylphosphoramide, etc. or a mixture thereof.

The reaction temperature is not critical, and the reaction is in many cases conducted under cooling, at ambient temperature or under heating.

Process 4

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to removal reaction of the carboxy-protective group in R_6^2.

This reaction is carried out by a conventional method such as hydrolysis, reduction, and the like.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, solvent, etc.) are substantially the same as those illustrated for removal reaction of the carboxy-protective group of the compound (Ia) in Process 2, and therefore are to be referred to said explanation.

The object compound (I) can be converted into its pharmaceutically acceptable salt in a conventional manner.

The processes for the preparation of the starting compound are explained in detail in the following.

Process A

The compound (IVb) or a salt thereof can be produced by reacting the compound (IVa) or a reactive derivative at the carboxy group thereof, or a salt thereof with the compound (V) or a reactive derivative at the hydroxy group, or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (IVa) may include the same ones as exemplified for the compound (Ib) in Process 3.

Suitable reactive derivative at the hydroxy group of the compound (V) may include the compound (V) whose hydroxy group is substituted by an acid residue such as halogen (e.g. chlorine, bromine, iodine, etc.), or the like.

Suitable salts of the compounds (IVa) and (IVb) may include the same salt as exemplified for the compound (I), and suitable salt of the compound (V) may include the same salt with a base as exemplified for the compound (I).

This reaction is carried out by the same method as that illustrated for Process 3, and therefore, the reaction conditions (e.g. reaction temperature, solvent, base, etc.) are to be referred to said explanation.

Process B— 1

The compound (VII) or a salt thereof can be produced by reacting the compound (IV) or a reactive derivative at the amino group thereof, or a salt thereof with the compound (VI) or a reactive derivative at the carboxy group thereof or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IV) may include a conventional one, for example, a silyl derivative formed by the reaction of the compound (IV) with a silyl compound such as trimethylsilylacetamide, bis(trimethylsilyl)acetamide, bis(trimethylsilyl)urea, and the like, and suitable reactive derivative of the compound (VI) may include an acid halide such as acid chloride, acid bromide, or the like, which can be prepared by the reaction of diketene and halogen.

Suitable salt of the compound (IV) may include the same salt as exemplified for the compound (I), and suitable salts of the compounds (VI) and (VII) may include the same salt with a base as exemplified for the compound (I).

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, acetone, dioxane, acetonitrile, chloroform, benzene, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine, hexamethylphosphoramide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under cooling to warming.

Process B— 2

The compound (II) or a salt thereof can be produced by reacting the compound (VII) or a salt thereof with a nitrosating agent.

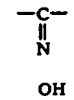
Suitable nitrosating agent may include nitrous acid and its conventional derivatives such as nitrosyl halide (e.g. nitrosyl chloride, nitrosyl bromide, etc.), alkali metal nitrite (e.g. sodium nitrite, potassium nitrite, etc.), alkyl nitrite (e.g. butyl nitrite, pentyl nitrite, isoamyl nitrate, etc.), and the like.

In case that a salt of nitrous acid or its alkali metal salt is used as a nitrosating agent, the reaction is preferably carried out in the presence of an acid such as an inorganic or organic acid (e.g. hydrochloric acid, sulfuric acid, formic acid, acetic acid, etc.).

This reaction can preferably be carried out in the presence of an activated methylene compound such as acetylacetone, ethyl acetoacetate, and the like.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, acetic acid, benzene, methanol, ethanol, tetrahydrofuran, methylene chloride, or a mixture thereof. The reaction temperature is not critical and the reaction is preferably conducted within the range of cooling to an ambient temperature.

The compound (II) of this reaction may include syn isomer, anti isomer and a mixture thereof at the hydroxyimino group thereof, and such compound may be represented by the partial formula:



The object compound (I) and the pharmaceutically acceptable salt thereof of the present invention are novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms including Gram-positive and Gram-negative microorganisms and are useful as antimicrobial agents, especially for oral administration.

Now in order to show the utility of the object compound (I), the test data on the urinary excretion of a representative compound (I) of this invention are shown in the following.

Urinary Excretion Test

(1) Test Method

Test compound (100 mg/kg) was given orally to groups of three rats, and urinary samples were collected at 0 to 24 hours.

(2) Test Compound

(A) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (hereinafter referred to as Compound A)

(B) 1-DL-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (hereinafter referred to as Compound B)

(3) Test Result

Percentage of urinary excretion value is shown in the following table.

Compound	Urinary Excretion (%)
A	54.09
B	26.0

For therapeutic administration, the object compound (I) and the pharmaceutically acceptable salt thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compound (I) to be applied, etc. In general, amounts between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg of the object compound (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for the purpose of illustrating the present invention.

Preparation 1

1-DL-Iodoethyl ethyl carbonate (7.32 g) was added all at once to a solution of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (4.52 g) and 1,8-Diazabicyclo[5,4,0]undec-7-en (4.5 ml) in N,N-dimethylacetamide (45 ml) under ice-cooling. After the mixture was stirred for 45 minutes at 0°–3° C., the reaction mixture was poured into ice-water (200 ml) and extracted with ethyl acetate (200 ml). The organic extract was washed with water and brine, dried over magnesium sulfate and concentrated to one fourth volume of its original one. The concentrate was added to concentrated hydrochloric acid (2 ml). The resulting precipitate was collected by filtration, washed with ethyl acetate and air-dried to give DL-1-ethoxycarbonyloxyethyl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (2.66 g).

IR (Nujol) cm^{-1}: 3400, 1775, 1755, 1720

NMR (DMSO-d_6) δ: 1.27 (3H, , J=7 Hz), 1.53 (3H, d, J=6 Hz), 3.93 (2H, m), 4.23 (2H, q, J=7 Hz), 5.0–6.0 (4H, m), 6.7–7.2 (2H, m), 8.0–10.0 (2H, broad m).

Preparation 2

Benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (150 g) and trimethylsilylacetamide (189 g) was dissolved in ethyl acetate (1.5 liter), and the solution was cooled to −20° C. Thereto was added 4-bromoacetoacetic bromide, which was obtained from diketene (39 g) and bromine (75 g) in methylene chloride (200 ml) at −20° C., and the mixture was stirred at −10° C. for an hour. The reaction mixture was poured into a mixture of methylene chloride (2 liter) and water (1 liter), and the organic layer was separated, followed by washing with water and an aqueous sodium chloride. After the solvent was removed in vacuo, the resultant precipitates were washed with ethyl acetate and then dried to give benzhydryl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (171 g), mp 133°–137° C. (dec.).

IR (Nujol) cm^{-1}: 3270, 1765, 1705, 1650, 1550

NMR (DMSO-d_6) δ: 3.5–4.5 (6H, m), 5.2–6.0 (4H, m), 6.83 (1H, m), 7.00 (1H, s), 7.45 (10H, m), 9.25 (1H, d, J=8 Hz)

Preparation 3

The following compound was obtained according to a similar manner to that of Preparation 2.

DL-1-Ethoxycarbonyloxyethyl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate

IR (Nujol) cm^{-1}: 1780, 1760, 1270, 1080

NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7 Hz), 1.53 (3H, d, J=6 Hz), 3.93 (2H, m), 4.17 (2H, s), 4.23 (2H, q, J=7 Hz), 4.33 (2H, s), 5.0–6.0 (4H, m), 6.5–7.2 (2H, m), 9.17 (1H, d, J=8 Hz)

Preparation 4

To a solution of benzhydryl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (40 g) in methylene chloride (400 ml) and acetic acid (200 ml) was added dropwise a solution of sodium nitrite (7.5 g) in water (50 ml) at −10° to −5° C., and the mixture was stirred at −5° C. for 30 minutes. After addition of urea (7 g) and stirring at ambient temperature for 30 minutes, water (400 ml) was added to the reaction mixture. The organic layer was separated, washed with water and 10% aqueous sodium chloride, and dried over magnesium sulfate.

Removal of the solvent gave the solid, which was dried in vacuo to obtain benzhydryl 7-(4-bromo-2-hydroxyiminoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (48 g), mp 105°–108° C.

IR (Nujol) cm^{-1}: 3250, 1770, 1705, 1655, 1540

NMR (DMSO-d_6) δ: 3.80 (2H, m), 4.67 (2H, s), 5.2–6.2 (4H, m), 6.80 (1H, m), 7.00 (1H, s), 7.45 (10H, m), 9.42 (1H, d, J=8 Hz), 13.20 (1H, s)

EXAMPLE 1

To a solution of benzhydryl 7-(4-bromo-2-hydroxyiminoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (48 g) in N,N-dimethylacetamide (200 ml) was added thiourea (7.0 g) at 5° C., and the mixture was stirred at ambient temperature for an hour. After the reaction mixture was poured into 3% aqueous sodium bicarbonate (2 liter), sodium chloride (150 g) was added thereto. The precipitates were collected by filtration and then dissolved in a mixture of acetone (200 ml) and ethyl acetate (500 ml). The separated organic layer was washed with an aqueous sodium chloride, followed by evaporation. The resultant precipitates were collected by filtration, washed with ethyl acetate and diethyl ether and dried in vacuo to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (16.9 g), mp 133°–136° C.

IR (Nujol) cm^{-1}: 3200, 1780, 1720, 1670, 1610

NMR (DMSO-d_6) δ: 3.75 (2H, m), 5.2–6.1 (4H, m), 6.67 (1H, s), 6.75 (1H, m), 7.00 (1H, s), 7.20 (2H, m), 7.34 (10H, m), 9.50 (1H, d, J=8 Hz)

EXAMPLE 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) DL-1-Ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3300, 1780, 1750, 1670

NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7 Hz), 1.50 (3H, d, J=6 Hz), 3.75 (2H, m), 4.13 (2H, q, J=7 Hz), 5.1–6.0 (4H, m), 6.63 (1H, s), 6.7–7.3 (4H, m), 9.45 (1H, d, J=8 Hz), 11.33 (1H, s)

(2) t-Butoxycarbonylmethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3300, 3170, 1780, 1730, 1665, 1620

(3) DL-1-Propionyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3300, 3200, 1780, 1765, 1720, 1710, 1660, 1630

(4) Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3400, 1785, 1750, 1670, 1615, 1530, 1310, 1220

(5) Palmitoyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3300, 1775, 1670, 1615, 1530, 1305, 1210

(6) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3300, 1812, 1772, 1730, 1668, 1611

(7) Phthalid-3-yl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3200 (broad), 1772 (broad), 1728 (shoulder), 1660, 1620

(8) Carboxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 1765 (broad), 1720, 1660 (broad)

(9) Sodium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)

IR (Nujol) cm^{-1}: 3200, 1760, 1660, 1600

EXAMPLE 3

Benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (68.5 g) was added portionwise to a mixture of 2,2,2-trifluoroacetic acid (60 ml) and anisole (60 ml) at 5°–7° C., and the mixture was stirred at 5° C. for an hour. The reaction mixture was added dropwise to diisopropyl ether (1.5 liter), followed by collecting the precipitates by filtration. After dissolving in a mixture of tetrahydrofuran (100 ml) and ethyl acetate (100 ml), the solution was extracted with an aqueous sodium bicarbonate. The obtained aqueous layer was adjusted to pH 5.0 with 10% hydrochloric acid, washed with ethyl acetate and then chromatographed on aluminum oxide. Elution was carried out by 3% aqueous sodium acetate, and the fractions containing the desired compound were collected. After adjusting to pH 6.0 with 10% hydrochloric acid, the aqueous solution was again chromatographed on activated charcoal. Elution was carried out by 20% aqueous acetone, and the collected fractions were concentrated in vacuo and then lyophilized to give sodium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (14.4 g), which was decomposed from 220° C.

IR (Nujol) cm^{-1}: 3200, 1760, 1660, 1600

NMR (D_2O) δ: 3.67 (2H, s), 5.2–5.7 (3H, m), 5.83 (1H, d, J=5 Hz), 6.80 (1H, m), 7.00 (1H, s)

EXAMPLE 4

1-DL-Iodoethyl ethyl carbonate (22 g) was added dropwise to a solution of sodium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (15 g) in N,N-dimethylacetamide (120 ml) at 5°–7° C., and the mixture was stirred at 5° C. for 30 minutes. To the reaction mixture was added ethyl acetate (200 ml), followed by filtration. The filtrate was washed with water and an aqueous sodium chloride,

and then dried over magnesium sulfate. After removal of the solvent, the residue was washed with ethyl acetate and dried in vacuo to give DL-1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (7.4 g), mp 126°–130° C.

IR (Nujol) cm^{-1}: 3300, 1780, 1750, 1670, 1620

NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7 Hz), 1.50 (3H, d, J=6 Hz), 3.75 (2H, m), 4.13 (2H, q, J=7 Hz), 5.1–6.0 (4H, m), 6.65 (1H, s), 6.7–7.3 (4H, m), 9.45 (1H, d, J=8 Hz), 11.33 (1H, s)

EXAMPLE 5

Cesium carbonate (2.06 g) was added to a solution of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (5 g) in N,N-dimethylacetamide (50 ml) at 25° C.

The mixture was stirred at ambient temperature for 1 hour and cooled on an ice-bath. To this cooled mixture was added 1-DL-iodoethyl ethyl carbonate (9.2 g) all at once, and the mixture was stirred at 0°–3° C. for 40 minutes. To the reaction mixture was added ethyl acetate (300 ml), which was followed by filtration. The filtrate was washed with water twice and brine, treated with activated charcoal and dried over magnesium sulfate. After removal of the solvent in vacuo, the residue was washed with diisopropyl ether and air-dried to give DL-1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (4.6 g), mp 126°–130° C.

IR (Nujol) cm^{-1}: 3300, 1780, 1750, 1670

NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7 Hz), 1.50 (3H, d, J=6 Hz), 3.75 (2H, m), 4.13 (2H, q, J=7 Hz), 5.1–6.0 (4H, m), 6.63 (1H, s), 6.7–7.3 (4H, m), 9.45 (1H, d, J=8 Hz), 11.33 (1H, s).

EXAMPLE 6

Potassium iodide (4.0 g) was added to a solution of t-butyl chloroacetate (1.2 g) in N,N-dimethylacetamide (50 ml) and the mixture was stirred for 40 minutes at ambient temperature. The precipitate was filtered off. To the filtrate was added potassium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (3.2 g) at ambient temperature and the mixture was stirred for 1.5 hours at the same temperature. The reaction mixture was added to a mixture of water and ethyl acetate and the mixture was adjusted to pH 7.0 with 20% aqueous solution of potassium carbonate. The separated organic layer was washed with water, dried over magnesium sulfate and evaporated to give t-butoxycarbonylmethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (2.0 g).

IR (Nujol) cm^{-1}: 3300, 3170, 1780, 1730, 1665, 1620

NMR (DMSO-d_6) δ: 1.43 (9H, s), 3.76 (2H, q, J=18.0 Hz), 4.73 (2H, s), 5.24 (1H, d, J=5.0 Hz), 5.38 (1H, d, J=11.0 Hz), 5.68 (1H, d, J=18.0 Hz), 5.82 (1H, dd, J=5.0 Hz, 8.0 Hz), 6.66 (1H, s), 7.03 (1H, dd, J=11.0 Hz, 18.0 Hz), 9.46 (1H, d, J=8.0 Hz).

EXAMPLE 7

DL-1-Propionyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.38 g) was obtained by reacting 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (5 g) with DL-1-bromoethyl propionate (4.56 g) according to a similar manner to that of Example 5.

IR (Nujol) cm^{-1}: 3300, 3200, 1780, 1765, 1720, 1710, 1660, 1630

NMR (DMSO-d_6) δ: 1.03 (3H, t, J=7 Hz), 1.48 (3H, d, J=6 Hz), 2.38 (2H, q, J=7 Hz), 3.53 and 3.97 (2H, ABq, J=18 Hz), 5.23 (1H, d, J=5 Hz), 5.4 (1H, d, J=11 Hz), 5.65 (1H, d, J=18 Hz), 5.85 (1H, dd, J=8 Hz, 5 Hz), 6.67 (1H, s), 6.83 (1H, dd, J=18 Hz, 11 Hz), 6.93 (1H, q, J=6 Hz), 7.1 (2H, broad s), 9.43 (1H, d, J=8 Hz), 11.33 (1H, s).

EXAMPLE 8

Pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.24 g) was obtained by reacting 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (3 g) with iodomethyl pivalate (5.05 g) according to a similar manner to that of Example 5, mp 90°–100° C. (dec.).

IR (Nujol) cm^{-1}: 3400, 1785, 1750, 1670, 1615, 1530, 1310, 1220

NMR (DMSO-d_6) δ: 1.14 (9H, s), 3.58 and 3.97 (2H, ABq, J=18 Hz), 5.24 (1H, d, J=5 Hz), 5.39 (1H, d, J=11 Hz), 5.7–6.0 (3H, m), 5.77 (1H, d, J=17 Hz), 6.70 (1H, s), 6.83 (1H, dd, J=11 Hz, 17 Hz), 7.12 (2H, broad s), 9.49 (1H, d, J=8 Hz), 16.24 (1H, s)

EXAMPLE 9

Palmitoyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.86 g) was obtained by reacting 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (3 g) with iodomethyl palmitate (4.13 g) according to a similar manner to that of Example 5, mp 90°–105° C. (dec.)

IR (Nujol) cm^{-1}: 3300, 1775, 1670, 1615, 1530, 1305, 1210

NMR (DMSO-d_6) δ: 1.1–1.7 (26H, m), 2.3–2.5 (2H, m), 3.56 and 3.95 (2H, ABq, J=18 Hz), 5.21 (1H, d, J=5 Hz), 5.37 (1H, d, J=11 Hz), 5.7–6.0 (3H, m), 5.75 (1H, d, J=17 Hz), 6.66 (1H, s), 6.7–7.0 (1H, m)

EXAMPLE 10

To a solution of potassium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (2.0 g) in N,N-dimethylacetamide (30 ml) was added 4-bromomethyl-5-methyl-1,3-dioxol-2-one (1.0 g) under ice-cooling with stirring. The reaction mixture was stirred at the same temperature for 30 minutes. The resulting mixture was poured into ethyl acetate (200 ml) and the organic solution was washed with water three times. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (50 g) to give (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (0.62 g).

IR (Nujol) cm^{-1}: 3300, 1812, 1772, 1730, 1668, 1611

NMR (DMSO-d_6) δ: 2.17 (3H, s), 3.52, 3.98 (2H, ABq, J=17 Hz), 5.15 (2H, s), 5.20 (1H, d, J=5 Hz), 5.30 (1H, d, J=11 Hz), 5.63 (1H, d, J=17 Hz), 5.76 (1H, dd, J=5 Hz, 8 Hz), 6.63 (1H, s), 6.83 (1H, dd, J=11 Hz, 17Hz), 9.42 (1H, d, J=8 Hz), 11.3 (1H, s).

EXAMPLE 11

Phthalid-3-yl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.05 g) was obtained by reacting potassium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.0 g) with 3-bromophthalide (0.9 g) according to a similar manner to that of Example 10.

IR (Nujol) cm^{-1}: 3200 (broad), 1772 (broad), 1728 (shoulder), 1660, 1620

NMR (DMSO-d_6) δ: 3.70 (2H, m), 5.18 (1H, d, J=5 Hz), 5.43 (1H, d, J=11 Hz), 5.73 (1H, d, J=17 Hz), 5.83 (1H, dd, J=5 Hz, 8 Hz), 6.75 (1H, s), 6.7–7.2 (2H, m), 7.66–8.0 (6H, m), 9.87 (1H, d, J=8 Hz)

EXAMPLE 12

Trifluoroacetic acid (5.4 ml) was added to a suspension of t-butoxycarbonylmethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.8 g) in methylene chloride (4 ml) and anisole (1.8 ml) at ambient temperature and the mixture was stirred for 2 hours at the same temperature.

To the resulting solution was added diisopropyl ether and the mixture was stirred. The resulting precipitates were collected by filtration and washed with diisopropyl ether. The precipitates were added to a mixture of ethyl acetate and water and the mixtuer was adjusted to pH 7 with 20% aqueous solution of sodium carbonate under stirring. The separated aqueous layer was adjusted to pH 2.2 with 10% hydrochloric acid under ice-cooling. The precipitate was collected by filtration, washed with ice-water and dried over phosphorus pentoxide in vacuo to give carboxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (0.73 g).

IR (Nujol) cm^{-1}: 1765 (broad), 1720, 1660 (broad)

NMR (DMSO-d_6) δ: 3.76 (2H, q, J=18.0 Hz), 4.76 (2H, s), 5.24 (1H, d, J=5.0 Hz), 5.37 (1H, d, J=11.0 Hz), 5.86 (1H, d, J=17.0 Hz), 7.83 (1H, dd, J=5.0 Hz, 8.0 Hz), 6.69 (1H, s), 6.61–7.67 (3H, m), 9.50 (1H, d, J=8.0 Hz).

EXAMPLE 13

To a solution of DL-1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1 g) in a mixture of ethyl acetate (50 ml) and ethanol (2 ml) was added concentrated hydrochloric acid (0.3 ml) under ice-cooling, and the mixture was stirred for 10 minutes at 0°–3° C. To the solution was added diisopropyl ether (50 ml), and the resulting precipitate was collected by filtration, washed with ethyl acetate and air-dried to give DL-1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate hydrochloride (syn isomer) (0.8 g).

IR (Nujol) cm^{-1}: 3100, 1780, 1750, 1640

NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz), 1.53 (3H, d, J=6 Hz), 3.75 (2H, m), 4.20 (2H, q, J=7 Hz), 5.0–6.0 (6H, m), 6.83 (1H, s), 6.7–7.2 (2H, m), 9.7 (1H, d, J=8 Hz), 12.5 (1H, broad s)

EXAMPLE 14

To a solution of benzhydryl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (10 g) in a mixture of methylene chloride (70 ml) and acetic acid (25 ml) was dropwise added isoamyl nitrite (3.5 ml) at −3° to −5° C. The mixture was stirred for 40 minutes at −5° C., followed by addition of acetylacetone (4 g) and stirring for 30 minutes at 5° C. To the reaction mixture was added thiourea (3 g) and after stirring for 3 hours, thereto were added dropwise ethyl acetate (70 ml) and diisopropyl ether (100 ml). The resultant precipitate was collected by filtration and dried in vacuo to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate hydrobromide (syn isomer) (11.7 g). 3 g of this product was added portionwise to a mixture of 2,2,2-trifluoroacetic acid (5 ml) and anisole (5 ml) at 5° to 7° C. After stirring for 1 hour at 5° C., the reaction mixture was added dropwise to diisopropyl ether (150 ml). The resultant precipitate was collected by filtration and dissolved in a mixture of tetrahydrofuran (10 ml) and ethyl acetate (10 ml). The organic layer was extracted with an aqueous sodium bicarbonate. The aqueous extract was washed with ethyl acetate under keeping the pH value at 5 and then adjusted to pH 2.2 with 10% hydrochloric acid. This solution was stirred for 1 hour at 0° C., and the obtained crystals were collected by filtration and dried in vacuo to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (0.79 g).

IR (Nujol) cm^{-1}: 3300, 1780, 1665, 1180, 1130

EXAMPLE 15

To a solution of benzhydryl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (15 g) in a mixture of methylene chloride (100 ml) and acetic acid (30 ml) was added dropwise a solution of sodium nitrite (2.8 g) in water (5 ml) at −10° to −15° C. The reaction mixture was stirred for 40 minutes at −5° C., followed by addition of acetylacetone (4 g) and then stirring for further 15 minutes at ambient temperature. The reaction mixture was poured into a mixture of water (200 ml) and methylene chloride (200 ml), and the organic layer was separated and washed with water. The solution was evaporated and the residue was dissolved in N,N-dimethylacetamide (40 ml). To this solution was added thiourea (3.4 g), and the mixture was stirred for 1 hour at ambient temperature, and poured into a mixture of tetrahydrofuran (150 ml), ethyl acetate (300 ml) and water (300 ml). The mixture was adjusted to pH 6.0 with 20% aqueous sodium hydroxide. The separated organic layer was washed with 20% aqueous sodium chloride successively and dried over magnesium sulfate. The solvent was removed by distillation in vacuo, and the precipitate was collected by filtration and washed with ethyl acetate and diisopropyl ether. This precipitate was dried in vacuo to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (8.5 g).

IR (Nujol) cm^{-1}: 3200, 1780, 1720, 1670, 1610

EXAMPLE 16

To a solution of benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (5 g) in a mixture of anisole (20 ml) and acetic acid (5 ml) was added dropwise boron trifluoride etherate (5 ml) at 10° C. After stirring for 20 minutes at 10° C., the reaction mixture was poured into a mixture of tetrahydrofuran (100 ml), ethyl acetate (100 ml) and water (100 ml), and then adjusted to pH 6.0 with 20% aqueous sodium hydroxide. The resultant aqueous layer was separated and washed with ethyl acetate under keeping the pH value at 6.0. This solution

was subjected to chromatography on aluminum oxide. The fractions eluted with 3% aqueous sodium acetate were collected and adjusted to pH 4.0 with 10% hydrochloric acid. This solution was further chromatographed on nonionic adsorption resin "Diaion HP-20" (Trademark, manufactured by Mitsubishi Chemical Industries). The fractions eluted with 20% aqueous acetone were collected, concentrated in vacuo and adjusted to pH 2.0 with 10% hydrochloric acid. The resultant precipitate was collected by filtration and dried in vacuo to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (1.23 g).

IR (Nujol) cm^{-1}: 3300, 1780, 1665, 1180, 1130

NMR (DMSO-d_6) δ: 3.76 (2H, ABq, J=18 Hz), 5.2–6.0 (4H, m), 6.73 (1H, s), 6.8–7.50 (3H, m), 9.5 (1H, d, J=8 Hz), 11.4 (1H, broad s)

EXAMPLE 17

(1) Benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (1 kg) and 1,3-bis(trimethylsilyl)urea (1.46 kg) was dissolved in tetrahydrofuran (8 l) and the mixture was cooled to −20° C. To this solution was added 4-bromoacetoacetyl bromide obtained from diketene (224 ml) and bromine (147 ml) in methylene chloride at −20° C. and the mixture was stirred for 30 minutes at −15° C. The reaction mixture was poured into a mixture of ethyl acetate (12 l) and water (6 l). The organic layer was separated, washed with an aqueous sodium chloride, and then evaporated in vacuo. The resultant precipitate was stirred in diisopropyl ether (10 l) for 1 hour at 0° C., and the obtained crystals were collected by filtration and dried in vacuo to give benzhydryl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (1.27 kg), mp 133°–137° C. (dec.).

(2)

To a solution of benzhydryl 7-(4-bromoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (500 g) in a mixture of methylene chloride (4.5 l) and acetic acid (1.7 l) was added dropwise a solution of sodium nitrite (93.2 g) in water (450 ml) at −15° to −22° C. The reaction mixture was stirred for 7 minutes at −15° C., followed by addition of ethyl acetoacetate (117 g) and then stirring for 5 minutes at ambient temperature. The reaction mixture was washed with water (6 l×2) and an aqueous sodium chloride (6 l). To the separated organic layer was added thiourea (82.2 g) dissolved in N,N-dimethylacetamide (1 l), and the mixture was stirred for 1 hour at 36° C. After methylene chloride was removed in vacuo, the residual oil was poured into a mixture of tetrahydrofuran (3.5 l), ethyl acetate (7 l) and ice-water (4 l). This mixture was adjusted to pH 6.0 with 10% aqueous sodium hydroxide. The separated organic layer was washed with water (4 l×2) and an aqueous sodium chloride. The solvent was removed by distillation in vacuo and the residual crystals were stirred in a mixture of ethyl acetate (1.6 l) and diisopropyl ether (2.4 l) for 1 hour at 0° C. The crystals obtained were collected by filtration to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (394.5 g).

IR (Nujol)cm^{-1}: 3200, 1780, 1720, 1670, 1610

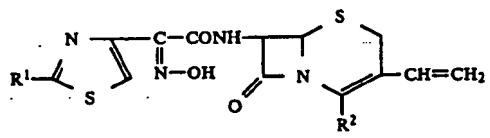
EXAMPLE 18

DL-1-Acetoxyethyl 7[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) (1.12 g) was obtained by reacting 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (5 g) with DL-1-bromoethyl acetate (3.42 g) in the presence of cesium carbonate (2.04 g) according to a similar manner to that of Example 5.

I.R. (Nujol)cm^{-1}: 3300, 1780, 1760, 1670, 1210

What we claim is:

1. A syn isomer of the compound of the formula:



(I)

in which

R^1 is amino or a protected amino group, and

R^2 is carboxy or a protected carboxy group,

and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein R^1 is amino.

3. A compound of claim 2, which is 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) or its sodium salt or its potassium salt.

4. A compound of claim 2, wherein R^2 is esterified carboxy group.

5. A compound of claim 4, wherein R^2 is lower alkoxycarbonyloxy(lower)alkoxycarbonyl.

6. A compound of claim 5, which is 1-ethoxycarbonyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) or its hydrochloride.

7. A compound of claim 4, wherein R^2 is lower alkoxycarbonyl(lower)alkoxycarbonyl.

8. A compound of claim 7, which is tert-butoxycarbonylmethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

9. A compound of claim 4, wherein R^2 is carboxy(lower)alkoxycarbonyl.

10. A compound of claim 9, which is carboxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

11. A compound of claim 4, wherein R^2 is lower alkanoyloxy(lower)alkoxycarbonyl.

12. A compound of claim 11, which is 1-propionyloxyethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

13. A compound of claim 11, which is pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

14. A compound of claim 4, wherein R^2 is higher alkanoyloxy(lower)alkoxycarbonyl.

15. A compound of claim 14, which is palmitoyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

16. A compound of claim 4, wherein R^2 is (5-lower alkyl-2-oxo-1,3-dioxol-4-yl) (lower)alkoxycarbonyl.

17. A compound of claim 16, which is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

18. A compound of claim 4, wherein R^2 is phthalidyloxycarbonyl.

19. A compound of claim 18, which is phthalid-3-yl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer).

20. A pharmaceutical antimicrobial composition which comprises an antimicrobially effective amount of a compound of claim 1 and a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

* * * * *

EXHIBIT 5

MAINTENANCE FEE RECEIPTS

Patent Maintenance Fees - Public Inquiry

Patent#: 4559334 Filed: 10/20/83 Issued: 12/17/85 Serial#: 06543880
Status: 4th, 8th And 12th Year Fees Paid Sml Entity: NO
Window Opens: Surchg Due: Expiration:
Fee Amt Due:$ Surchg Amt Due:$ Total Amt Due:$
Fee Code: Surchg Code:
Title: 7-SUBSTITUTED-3-VINYL-3-CEPHEM COMPOUNDS AND PROCESSES FOR PRODUCTION OF THE SAME

Address For Fee Purposes:
COMPUTER PATENT ANNUITIES
901 N. WASHINGTON STREET
SUITE 305
ALEXANDRIA VA 22314

Most Recent Significant Events:

06/05/97	Payment of Maintenance Fee, 12th Year, Large Entity
06/03/93	Payment of Maintenance Fee, 8th Year, Large Entity
04/03/89	Payment of Maintenance Fee, 4th Year, PL 97-247
02/03/86	Payor Number Assigned
	Last Event On Maintenance History

EXHIBIT 6

IND SUBMISSION LETTER

PARKE-DAVIS
Pharmaceutical Research Division
Warner-Lambert Company

April 30, 1990

Serial No. 000
CI-983 Capsules

Re: Original IND

Food and Drug Administration
Center for Drug Evaluation
and Research
Central Document Room
12420 Parklawn Drive
Park Building, Room 214
Rockville, Maryland 20852

Dear Sir or Madam:

Pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 312.20, an Investigational New Drug Application for CI-983 Capsules, a cephalosporin antibacterial agent, is submitted in triplicate.

Warner-Lambert has licensed CI-983 from Fujisawa Pharmaceutical Company, Osaka, Japan. A marketing application was submitted in Japan in December 1989 and is under review.

The initial work to be done under this IND will be a Phase 1 study in the United States. CI-983 Capsules will not be administered to humans before 30 days from the official date of receipt of this submission.

If there are any questions or comments on this submission, please contact me at (313) 996-1819, or Dr. Howard Holden at (313) 996-5141.

Sincerely,

Drusilla L. Scott, Ph.D.
Manager, Worldwide Regulatory Affairs

220901.bf

Attachments

EXHIBIT 7

IND ACKNOWLEDGMENT LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 34,738

Date MAY 8 1990

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 481052430

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 34,738

Sponsor: Parke-Davis Pharmaceutical Research

Name of Drug: CI-983

Date of Submission: April 30, 1990

Date of Receipt: May 2, 1990

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations) Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows.

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-520)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Kathy Huntley Consumer Safety Officer at (301) 443-0257.

Sincerely yours,

for Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-520 - yellow
HFD-520/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT 8

NDA SUBMISSION LETTER

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

September 3, 1996

NDA 50-739
Ref. No. 1
Omnicef™ (cefdinir) Capsules

Re: Original New Drug Application
User Fee I.D. No. 2566

Food and Drug Administration
Document and Records Section
12420 Parklawn Drive
Rockville, Maryland 20852

Dear Sir/Madam:

In accordance with Section 507 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, Parke-Davis is submitting a New Drug Application (NDA) for Omnicef™ (cefdinir) 300 mg Capsules for the treatment of mild to moderate bacterial infections in an outpatient setting. NDA 50-739 was preassigned on May 21, 1996.

As required under the Prescription Drug User Fee Act, 50% of the 1996 application fee ($102,000) has been sent to the Food and Drug Administration in care of Mellon Bank, Pittsburgh, Pennsylvania on August 15, 1996. The User Fee cover sheet is attached; our Identification Number is 2566.

This submission contains an archival copy containing 427 volumes and review copies for each technical reviewer. A field copy of Item 3 (Chemistry, Manufacturing, and Controls) has been sent to the FDA District Office in Newark, New Jersey in accordance with 21 CFR 314.440. Letters that authorize FDA to reference Drug Master Files (DMFs) are compiled in Section 1.1 of Item 3 as well as included in the sections that discuss the subject of the DMF.

"Omnicef" is the trade name selected for cefdinir. At their April 11, 1995 meeting, the CDER Labeling and Nomenclature Committee indicated that they would not object to this trademark.

Patent information and the Generic Drug Act certification in Item 13 are located in Volume 1.1 of the NDA, immediately preceding Item 1, NDA Index.

The studies that support the approval of Omnicef™ (cefdinir) Capsules were conducted under IND 34,738, submitted to the Division of Anti-infective Drug Products on May 2, 1990.

Summary minutes and dates of meetings (including the End-of-Phase 2 and pre-NDA meetings), and other significant discussions on clinical issues are included in Item 8.4 of the NDA, "Background/Overview of the Cefdinir Development Program."

Parke-Davis plans to submit an NDA for an oral suspension formulation of cefdinir for pediatric use in December 1996. The clinical data that supports pediatric use is included in NDA 50-739 as some of the pediatric and adult indications are the same and rely on one study in each population. Data from studies that support the only unique pediatric indication, acute suppurative otitis media, are also included as they are part of the integrated database. Inclusion of this information should also facilitate the clinical review when the oral suspension NDA is submitted.

The oral suspension NDA will, therefore, consist primarily of chemistry, manufacturing, and control information on the suspension product and the report of a relative bioavailability study between the drug supplies used in clinical trials and market image product. Updated safety information will also be included.

Finally, the NDA for Omnicef™ (cefdinir) Capsules is available as an electronic regulatory submission. The major difference between the paper and electronic submission is that case report forms (CRFs) from Phase 2/3 studies are available electronically only. All CRFs from these studies, not just those required by 21 CFR 314.50(b)(2), are available. The Agency granted a waiver of the requirements for paper copies of CRFs in a July 10, 1996 letter, a copy of which is attached.

Minor differences between the submissions are noted below:

Paper Submission	Electronic Submission
- Brief Index precedes NDA Index	- No Brief Index
- NDA page numbers at top right corner of page	- No NDA page numbers; hyperlinks used to navigate through NDA
- A reference will be included only once within a technical section, even if cited more than once	- Reference is available each time it is cited via a hyperlink
- Case Report Tabulations may have different print dates on occasion, due to page replacement	- All Case Report Tabulations for a study will show a uniform generation date

If there are any questions or comments regarding the NDA, please contact me at 313/996-1819 or Dr. Tim Cunniff at 313/996-7091, FAX 313/998-3283. Dr. Sean Brennan may be contacted for issues related to Chemistry, Manufacturing and Controls at 313/996-7596, or Dr. Paul Chen at 313/996-2623, FAX 313/996-7890.

Sincerely,

Drusilla L. Scott, Ph.D.
Director, FDA Liaison
Worldwide Regulatory Affairs

DS\rm
t:\nda\50-739\090396.001

Enclosures
Attachments

NDA Copies

"Blue" Archive	Vol. 1.1 - 1.427
"Red" Chemistry	Vol. 1.1 - 1.11
"Yellow" Pharmacology	Vol. 1.1, 1.12 - 1.25
"Orange" Biopharmaceutics	Vol. 1.1, 1.26 - 1.46
"White" Microbiology	Vol. 1.1, 1.47 - 1.52
"Tan" Medical	Vol. 1.1, 1.53 - 1.360, 1.427
"Green" Biometrics	Vol. 1.1, 1.361 - 1.426
"Maroon" Field (Newark)	Vol. 1.2 - 1.9
Ms. Regina Brown	
"Maroon" Field (San Juan)	Vol. 1.2 - 1.9
Mr. Samuel Jones/Mr. Richard Dent	

EXHIBIT 9

NDA RECEIPT LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-739

Parke-Davis Pharmaceutical Research
Attention: Drusilla L. Scott, Ph.D.
Director, FDA Liasion
Worldwide Regulatory Affairs
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48106-1047

SEP 11 1996

Dear Dr. Scott:

We have received your new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Omnicef® (cefdinir) Capsules

Therapeutic Classification: Standard

Date of Application: September 3, 1996

Date of Receipt: September 4, 1996

Our Reference Number: 50-739

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act on in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102© of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Carmen DeBellas
Consumer Safety Officer
Telephone: (301) 827-2125

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

James D. Bona

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

EXHIBIT 10

IND LOG

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04128	0	Mon, Apr 30, 1990		Initial IND
			Volumes = 6 Item 1: Cover Sheet Item 2: Table of Contents Item 3: Introductory Statement Item 4: General Investigational Plan Item 5: Investigator's Brochure: RR-X 720-02745 Item 6: Protocol and Related Information PR. 983-001: A. Sedman, MD/E. Posvar, MD/A. Vassos, MD Item 7: Chemistry, Manufacturing and Controls Item 8: Microbiology, General Pharmacology, Pharmacokinetics and Toxicology (57) Research Reports submitted. Refer to Research Report list for RR #, date, author and title. Item 9: Previous Human Experience (3) Research Reports submitted. Refer to Research Report list for RR #, date, author and title. Item 10: Additional Information	
B04133		Tue, May 08, 1990		FDA Letter RE: Acknowledging Receipt (IND 34,739)
			RE: Acknowledgement of receipt of IND on 8-May-90; Number 34,738 assigned.	
		FDA		
B04133	1	Fri, Jun 08, 1990		Protocol Amendment (Change in Protocol)
			Amendment #1: PR. 983-001-000: 08-Jun-90: Provides revisions: 1. 800 MG not to be administered 2. Subjects to keep dialy diary 3. Additional 10CC blood to be withdrawn 4. If blood donated 2 months prior subject excluded 5. Asprin-containing or non-steroidal anti-inflammatory drugs prohibited two weeks prior to start of study 6. History of lactose intolerance, subjects excluded	
B04133	2	Wed, Aug 15, 1990		Protocol Amendment (Change in Protocol)
			Amendment #2: PR. 983-001-000: 08-Aug-90: An additional determination of complete blood count.	
B04133	3	Thu, Sep 06, 1990		Information Amendment (Pharmacology/Toxicology)
			(3) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.	
B04134	4	Fri, Sep 14, 1990		Letter RE: Investigator's Brochure
		M. Lumpkin, MD	CI-983 RE: Revised version of Investigator's Brochure that includes the results from segment II and III reproductive toxicity studies and will be provided to future investigators who evaluate this drug.	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

ProductName: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04134	5	Mon, Sep 24, 1990		Letter RE: Request for Meeting with FDA
			CI-983 RE: Request a meeting with the agency to discuss our proposed clinical development plan. The plan is attached, following a proposed meeting agenda and issues for discussion. Also attached; we would not discuss these at meeting, but are provided for background. 1. Copies of the planned protocol for the initial efficacy studies 2. A dose-range finding study in respiratory tract infection 3. Two urinary tract infection studies	
B04134	6	Mon, Oct 01, 1990		Letter RE: Chemistry, Manufacturing & Controls
		M. Lumpkin, MD	RE: CI-983-018-000 Updated Chemistry, Manufacturing & Controls; regarding our #2 capsules.	
B04134	7	Thu, Oct 11, 1990		Information Amendment (Clinical)
			(1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.	
B04135	8	Thu, Oct 18, 1990		Information Amendment (Pharmacology/Toxicology)
			(1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.	

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report Contents/Report No./	Report No.
B04135	9	Thu, Oct 25, 1990	Protocol Amendment (New Investigators)	
			PR. 983-002-001:	
			PR. 983-002-002:	
			PR. 983-002-003:	
			PR. 983-002-006:	
			PR. 983-002-008:	
			PR. 983-002-009:	
			PR. 983-002-010:	
			PR. 983-002-011:	
			PR. 983-002-012:	
			PR. 983-002-017:	
			PR. 983-002-018:	
			PR. 983-002-019:	
			PR. 983-016-006:	
			PR. 983-016-010	
			PR. 983-016-011	
			PR. 983-016-013	
			PR. 983-016-015:	
			PR. 983-016-017:	
			PR. 983-016-019:	
			PR. 983-016-021:	
			PR. 983-016-023:	
			PR. 983-016-030:	
			PR. 983-016-036:	
			PR. 983-016-041:	
B04135	10	Mon, Nov 05, 1990	Protocol Amendment (New Investigators)	
			PR. 983-002-004:	
			PR. 983-002-005:	
			PR. 983-002-007:	
			PR. 983-002-015:	
			PR. 983-002-016:	
			PR. 983-002-020:	
			PR. 983-016-003:	
			PR. 983-0016-012:	
			PR. 983-016-014:	
			PR. 983-016-022:	
			PR. 983-016-024:	
			PR. 983-016-035:	

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date	RE/ To: From:	Report Title/ Report No./ Contents/Report No./
B04135	11	Tue, Nov 13, 1990		Protocol Amendment (New Investigators/Change in Protocol)
				PR. 983-003-002: PR. 983-003-006: PR. 983-003-007: PR. 983-03-012: PR. 983-003-0013: PR. 983-003-014: PR. 983-003-015: PR. 983-002-027: PR. 983-016-002: PR. 983-016-004: PR. 983-016-025: PR. 983-016-027: PR. 983-016-038: PR. 983-016-040 Amendment #1: PR. 983-002-001:Changes to section 6.2 (dosage regimen) and 12 (publications of research findings). This amendment applies to all active centers in this multicenter study. Amendment #2: Pr. 983-002-027: Adds section 4.3 (criteria for exclusion of patients) to protocol. This amendment applies to the Canadian centers 983-002-024, 983-002-025, 983-002-026, 983-002-027 and 983-002-028 only.
B04136	12	Wed, Nov 21, 1990		Protocol Amendment (New Investigators)
				PR. 983-002-014: PR. 983-002-024: PR. 983-002-028: PR. 983-016-009: PR. 983-016-026: PR. 983-016-037: PR. 983-003-003: PR. 983-003-005: PR. 983-003-009: PR. 983-003-016: PR. 983-003-017:
B04136	13	Wed, Nov 28, 1990		Protocol Amendment (New Investigators)
				PR. 983-012-026: PR. 983-016-016: PR. 983-016-029:
B04136	14	Tue, Dec 11, 1990		Minutes of FDA Meeting
				Date: 27-Nov-90 RE: FDA Meeting to discuss the development of the cephalosporin CI-983

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

Ci#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date	RE/ To: From:	Report Title/ Report No./ Contents/Report No./
B04136	15	Tue, Dec 11, 1990		Protocol Amendment (New Investigators/Change in Protocol) PR. 983-002-023: PR. 983-016-032: PR. 983-016-034: PR. 983-016-042: PR. 983-003-011: Amendment #1: Pr. 983-003-016: PR. 983-003-017: 29-Oct-90: Eliminates males from the study population and increases the minimum age from 13 to 18. PR. 983-002-009: [redacted]
B04136	16	Tue, Dec 18, 1990		Protocol Amendment (New Investigators) PR. 983-016-033:
B04136	17	Mon, Dec 31, 1990		IB Update Reference 9 (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title. Reference 28 - [redacted]
B04136	18	Fri, Jan 04, 1991		Protocol Amendment (New Investigators) PR. 983-002-013: PR. 983-016-025: [redacted]
B04136	19	Fri, Jan 11, 1991		Protocol Amendment (New Investigators) PR. 983-016-044:
B04136	20	Fri, Jan 18, 1991		Protocol Amendment (New Investigators) PR. 983-003-018: PR. 983-002-006: [redacted]
B04136	21	Fri, Jan 25, 1991		Protocol Amendment (New Investigators) PR. 983-003-019: PR. 983-003-020: PR. 983-016-017: [redacted]

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No/ Contents/Report No/
B04136	22	Fri, Feb 01, 1991	Protocol Amendment (New Investigators) PR. 983-002-021: PR. 983-016-031:
B04136	23	Mon, Feb 04, 1991 M. Lumpkin, MD	Letter RE: Response to FDA Request for Information RE: Dr. Sherman requested copies of the case report forms for the three clinical studies in progress, included in this submission.
B04136	24	Fri, Feb 15, 1991	Protocol Amendment (Change in Protocol) Amendment #3 983-002: Changes are in italicized print in the attached copy of the amendment. Amendment #1: 983-016: Changes two sections which are underlined in the attached amendment.
B04136	25	Thu, Feb 28, 1991	Protocol Amendment (New Investigators) PR. 983-003-008:
B04136	26	Thu, Mar 07, 1991	Protocol Amendment (New Investigators) PR. 983-017-000:
B04136	27	Fri, Mar 15, 1991	Protocol Amendment (New Investigators) PR. 983-003-021: PR. 983-002-006: [redacted] PR. 983-016-009: [redacted]
B04136	28	Tue, Mar 26, 1991	Protocol Amendment (New Investigators) PR. 983-022-000:
B04136	29	Mon, Apr 01, 1991	Information Amendment (Clinical) (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04136	30	Tue, Apr 02, 1991	Safety Report Patient #001 (BLP) PR. 983-016-015 AE: Pseudomembranous colitis; laboratory tests confirmed C. difficile. AE #:001-0983-91002-00

IND/NDA/DMF#:	34,738	IND	Doc Type: FDA CORRESPONDENCE
			SubType: IND
CI#:	983	Sub Date:	4/30/90
Generic:		Appr Date:	
Product Name:	Cefdinir		

Barcode /Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04137	31 Thu, Apr 11, 1991		Protocol Amendment (Change in Protocol) & Information Amendment (Pharm/Tox)

Amendment #1: PR. 983-021-000: 07-Mar-91: Each subject will receive 400 MG of each CI-983 preparation.
This amendment is effective on approval by the Community Researach Clinic Institutional Review Board.
An abbreviated information amendment that describes the suspension follows the protocol and amendment. An abbreviated amendment describing the Parke-Davis capsule was submitted to the IND on March 26 (SN #028), and detailed information in the Fujisawa capsule was submitted in the original IND. Detailed amendments on the Parke-Davis capsule and suspension are in preparation for submission in the near future.
(4) Research Reports submitted.
Refer to Research Report list for RR #, date, author and title.

B04138	32 Thu, Apr 18, 1991		Protocol Amendment (New Investigators & Change in Protocol)

PR. 983-003-023:
PR. 983-002-009: [redacted]

Amendment #2: PR. 983-016-003:PR.983-016-007:PR. 983-016-017:PR. 983-016-022:PR. 983-016-024: PR. 983-016-025: PR. 983-016-037: PR. 983-016-038:01-Mar-91: Amendment increases enrollment at each study center to a maximum of 40 patients.

Amendment #3: PR. 983-016-007: PR. 983-016-024: PR. 983-016-037: 14-Mar-91: Provides for collection of blood and urine samples for assessment of pharmacokinetic parameters.

Amendment #4: PR. 983-002-007: PR. 983-002-010: PR. 983-002-018: 29-Jan-91: Raises the enrollment at each study center from 40 to 80 evaluable patients.

Amendment #5: Pr. 983-002-018: 25-Mar-91: Raises enrollment from 80 to 125 evaluable patients.

B04138	33 Thu, Apr 18, 1991		Information Amendment (CMC)
	M. Lumpkin, MD		

RE: Attached is an information amendment (RR-Reg 730-01623 and Reg 956-00111) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for CI-983 100 MG and 200 MG capsules.
Revised specifications and test methods for the drug substance are described in RR-Reg 730-01623. Validation of the new HPLC method for the determination of the drug substance purity is also included in the report.
The drug product was previously obtained from Fujisawa Pharmaceutical Company. Research RR-Reg 956-00111 discusses the manufacturing, control and packaging of [redacted] The composition of the Parke-Davis product is identical to that of Fujisawa. The report includes a description of the manufacturing process, specification and testing methods and packaging (Continued - see central file copy)

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04138	34	Thu, Apr 25, 1991		Protocol Amendment (New Investigators)
			PR. 983-003-004: PR. 983-003-010: PR. 983-003-026: PR. 983-003-027: PR. 983-016-041: [redacted] PR. 983-016-030: [redacted]	
B04139	35	Thu, Apr 25, 1991		Information Amendment (Pharmacology/Toxicology)
			(5) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.	
B04141	36	Thu, Apr 25, 1991		Follow-Up to Safety Report
			Please refer to our IND safety report of 04-02-91 (SN #030), in which a case of pseudomembranous colitis was reported. A revised reporting form for this adverse event (AE #001-0983-91002-00) is being submitted at this time. The only item being changed is 12D., in which "action taken" has been revised from "discontinued" to "none". This reflects the fact that, while CI-983 was discontinued in response to abdominal cramping and diarrhea, it was not discontinued in response to pseudomembranous colitis per se, since the patient had been switched to ciprofloxacin two days before laboratory confirmation of C. difficile. If there are further questions, please call, etc.. .	
B04141	37	Thu, May 02, 1991		Protocol Amendment (Change in Protocol)
			Amendment #1: PR. 983-022-000: 01-Apr-91: The exclusion criterion for serum ferritin levels during screening has been changed from "outside the range of 60 to 200 NG/ML or which differ by more than 15 NG/ML on repeat assay" to "outside the range of 40 to 200 NG/ML or which differ by more than 20% on repeat assay." The former criterion was too stringent; the modified range will exclude people with iron deficiency. Also, the subject population has been expanded from healthy males only to include women who have had a hysterectomy more than one year previously, and who fulfill all other criteria for the study.	
B04141	38	Thu, May 02, 1991		Protocol Amendment (New Investigators)
			PR. 983-003-022: PR. 983-002-012: See attachment of list of 23 new MD's	
B04141	39	Fri, May 10, 1991		Protocol Amendment (New Investigators)
			PR. 983-003-024: PR. 983-003-025: PR. 983-003-029: PR. 983-003-031:	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic:
Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04141	40	Fri, May 17, 1991 M. Lumpkin, MD S. Brennan, Ph.D.	Information Amendment (CMC) RE: Attached is an information amendment (Research Report #'s RAR910458 and RAR 901096) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for CI-983 200 MG capsules manufactured by Fujisawa Pharmaceutical Co., Ltd. on 22-Mar-91, Dr. Linda Sherman (FDA). In a telephone conversation with Dr. D. Scott (P-D), requested batch analysis, stability data and method validation data on the 200 MG capsules (lot 202601K). The method validation for the 200 MG capsules, according to Fujisawa, is the same as that included in the Appendix 14 (RAR900020), Volume 2 of the original IND submission. (Continued- see central file copy)
B04141	41	Fri, May 24, 1991	Protocol Amendment (New Investigators/Change in Protocol) PR. 983-003-030: PR. 983-016-023: [redacted] Addendum #2: PR. 983-016-042: 23-Apr-91: Addendum adds a section on pharmacokinetic measurements in spatum and plasma as an option. Addendum #3: 983-016-042: 23-Apr-91: Addendum adds a section on post-therapy visits to determine relapse. These addenda are for this site only.
B04141		Tue, May 28, 1991 D. Scott M. Lumpkin	FDA Letter RE: FDA Recommendations RE: Reference is made to your investigational new drug application (IND) submitted May 2, 1990, pursuant to section 507 of the Federal Food Drug and Cosmetic Act for use of CI-983 ("Cefdinir") capsules. We have completed our review of your May 2, 1990, submission and have the following recommendations with respect to the phase I study as well as any future studies. The following comments are specific with respect to the phase I study. (Continued - see central file copy)
B04141		Tue, May 28, 1991 S. Scott M. Lumpkin	FDA Letter RE: IND Submissions RE: Reference is made to your investigational new drug application (IND) submitted May 2, 1990, pursuant to section 507 of the Federal Food, Drug and Cosmetic Act for the use of CI-983 capsules. We also reference your submission of protocols (IND 34,738, SN #005) dated September 24, 1990, for the treatment of uncomplicated urinary tract infections and for the treatment of lower respiratory tract infections. This letter refers to our meeting on Nov. 27, 1990 and related telephone conversation between members of your staff and Dr. Linda Sherman on Oct. 8, 1990, Feb. 20, 1991, and most recently, Mar. 13, 1991. (Continued - see central file copy)
B04141	42	Fri, Jun 14, 1991	Protocol Amendment (New Investigators) PR. 983-003-028:

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date: To: From:	RE/Report Title/ Contents/Report No:	Report No:
B04141	43	Tue, Jun 18, 1991 M. Lumpkin, MD H. Holden	Letter RE: Protocol Amendment (New Protocol) RE: Please refer to IND 34,738 for our cephalosporin CI-983 under clinical investigation, and to our meeting held with members of your division on Nov. 27, 1990. At that meeting, a pediatric pharmacokinetic study was discussed that was to be conducted prior to pediatric efficacy trials. We also agreed that we would send a draft protocol for review before planning to initiate the study. This protocol is included in this submission, and desk copies are included for Dr. Linda Sherman and Dr. See Lam. This will be a single dose study of two concentrations of drug, 4 MG/KG and 8MG/KG; each concentration will be studies in 12 children. We have identified investigational sites which will be able to recruit both pediatric patients being treated for an infection. (Continued - see central file copy)	
B04141	44	Tue, Jun 18, 1991	Protocol Amendment (New Investigators) PR. 983-002-030:	
B04141	45	Tue, Jun 25, 1991 M. Lumpkin, MD D. Scott, Ph.D.	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-003-022: RE: On 01-Apr-91 (SN #029), we submitted a research report RR-Memo 724-00134. Research report number RR-Memo 724-00134 was inadvertently used twice therefore, we are requesting that you note the change of research report number to RR-Memo 724-00145. This report is being resubmitted at this time to correct your files. No text in the report has been changed.	
B04142	46	Wed, Jul 10, 1991 M. Lumpkin D. Scott	Information Amendment (Clinical) (1) Research Report submitted. Refer to Research Report list for RR #, date, author and title. RE: This is an interim analysis of three studies of CI-983 in adults and adolescents which are being conducted under IND 34,738. This analysis is submitted in partial fulfillment of the requirements for initiation of pediatric studies with CI-983, as agreed to in our meeting of 27-Nov-90 and your letter of 28-May-91 regarding the IND. The studies evaluated are two double-blind, randomized, comparative multicenter studies of CI-983 in the treatment of uncomplicated urinary tract infections (studies 983-2 and 983-3), and one open-label, dose-finding, multicenter study in patients with lower respiratory tract infections (study 983-16). By the cutoff date of 28-Feb-91, 340 patients had entered these studies, and 272 completed treatment and the short-term follow-up visit. (Continued - see central file copy)	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04150	47	Wed, Jul 10, 1991	Protocol Amendment (New Investigators) PR. 983-002-008: [redacted] PR. 983-002-011: [redacted] PR. 983-002-018: [redacted] PR. 983-016-031: [redacted]
B04150	48	Tue, Jul 23, 1991	Annual Report Issue Date: 22-Jul-91
B04150	49	Wed, Jul 31, 1991 M. Lumpkin D. Scott	Letter RE: Information Amendment RE: Attached for your information and files are additions to a research report entitled, "Twenty-Six-Week Oral Toxicity Study of Cefdinir in Rats" dated 14-Mar-91 (RR 745-01758 which was filed under this IND on 25-Apr-91 (SN #49). [redacted] eplace pages I, 298 through 349, and insert new pages 350 through 377. These additions had no significant impact on the study results. [redacted]
B04150	50	Wed, Jul 31, 1991	Protocol Amendment (New Investigators) PR. 983-002-008: [redacted] PR. 983-016-025: [redacted]
B04150	51	Thu, Aug 15, 1991 M. Lumpkin S. Brennan	Letter RE: Response to FDA Request for Information RE: Please refer to our IND for cefdinir (CI-983), cephalosporin for oral administration. Cefdinir is being studied for its usefulness in the treatment of several types of community-acquired infections in adults and children. The data required to be submitted and reviewed prior to initiation of any pediatric work was outlined in your IND review letter of 28-May-91 (general comment 6). These items are cited below, along with the dates on which they were or are being submitted to the IND. (Continued - see central file copy)
B04150	52	Wed, Aug 21, 1991	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-016-027: [redacted] PR. 983-016-041: [redacted] Amendment #6: PR. 983-016: Increases enrollment from 20 to a maximum of 60 patients. Applies to centers 983-016-017, 983-016-024, 983-016-025, 983-016-033, 983-016-037 and 983-016-038. Amendment #2: CI-983-016: 18-Apr-91: Adding center 983-016-015 (SN #32).

Barcode / Ser / Ref#	Date / To / From:	RE / Report Title / Report No / Contents / Report No /
B04150 53	Wed, Aug 21, 1991	Information Amendment (Pharmacology/Toxicology)
		(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04150 54	Wed, Aug 21, 1991 M. Lumpkin	Letter RE: Information Amendment
		RE: In an information amendment (SN #33) to our IND 34,738 for cefdinir capsules submitted to you on 18-Apr-91, we updated the Chemistry, Manufacturing and Control information for the manufacture of 100 and 200 capsules of cefdinir by Parke-Davis [redacted] Attached is an information amendment to add the 300 MG/ capsules strength. The 300 MG capsules are compositionally proportional to the lower strengths of capsules (3 time and 1.5 times the net weights of 100 and 200 MG capsules respectively) since they are filled from the same granulation. The sample preparation in the assay of the 300 MG capsules is the same as reported in the above mentioned amendment (SN #33). (Continued - see central file copy)
	S. Brennan	
B04150 55	Wed, Aug 28, 1991 M. Lumpkin	Letter RE: Request for Meeting
		RE: We are studying the oral cephalosporin, cefdinir, under IND 34,738, and plan to initiate our major phase 3 program during the forth quarter of this year. At this time, we are requesting an end-of-phase 2 meeting, which we have discussed with Dr. Linda Sherman, the FDA Medical Reviewer, who agrees that a meeting in late October or early November would be appropriated. An outline of a proposed agenda is attached. A detailed agenda, clinical development plan, and proposed issues for discussion will be sent for your review about a month before the scheduled meeting. (Continued - see central file copy)
	D. Scott	
B04150 56	Wed, Aug 28, 1991	Protocol Amendment (New Investigators)
		PR. 983-003-033: PR. 983-002-022: [redacted] PR. 983-016-017: [redacted] PR. 983-016-024: [redacted]
B04150 57	Fri, Sep 13, 1991	Protocol Amendment (New Investigators & Change in Protocol)
		PR. 983-025-000: Conducted in Canada Amendment #1: PR. 983-025-000: 30-Aug-91: Specify 300 MG capsules under "Description of Medications"

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic:
Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04151	58	Thu, Sep 19, 1991 M. Lumpkin D. Scott	Letter RE: Information Amendment (Clinical) RE: We are submitting a final report on CI-983 and iron hemostasis (RR 720-02973). Parke-Davis has investigated whether cefdinir has any effect on iron hemeostasis in a number of in-vitro, animal, and clinical studies. This work has demonstrated conclusively that cefdinir does not cause significant changes in any non-invasive parameter of iron homeostasis.	
B04153	59	Thu, Sep 19, 1991 PR. 983-002-032: PR. 983-002-033: PR. 983-002-034: PR. 983-002-035: PR. 983-002-036: PR. 983-002-037:	Protocol Amendment (New Investigators)	
B04153	60	Thu, Sep 19, 1991 M. Lumpkin S. Brennan	Letter RE: Information Amendment (CMC) RE: Attached is an information amendment (RR-Reg 956-00113) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for cefdinir powder for oral suspension. In the IND amendment of 11-Apr-91 (SN #31), an oral suspension formulation of cefdinir was described. This formulation was used in Parke-Davis study 983-021-0 to determine its relative bioavailability to cefdinir capsules. On 13-Aug-91, the IND was amended (SN #51) to provide for a revised formulation. In the amendment, a brief description of the manufacturing and controls for the revised formulation were provided. At that time a commitment was made to provide a detailed manufacturing and controls section. (Continued - see file copy)	
B04153	61	Wed, Sep 25, 1991 M. Lumpkin D. Scott	Letter RE: Response to FDA Request for Information RE: As requested by Dr. Linda Sherman, we are outlining the protocol changes made in study 983-023-000: "A Single-Dose Safety Tolerance, and Pharmacokinetic Study of CI-983 in Pediatric Patients/Subjects", as described by telephone with Dr. Sherman, Dr. See Lam, and Mr. Carmen Debellas on 08-Aug-91 and in a brief follow-up conversation with Dr. Sherman on 09-Aug-91. Parke-Davis participants were Dr. Robert Guttendorf (Pharmacokinetics/Drug Metablism), Ms. Peggy Hawkins (Clinical Pharmacology), Dr. Drusilla Scott (Regulatory Affairs), and Dr. Artemios Vassos (Clinical Pharmacology). The items are listed below in the order they were discussed. (Continued - see file copy)	
B04153	62	Thu, Sep 26, 1991 	Protocol Amendment (New Investigators) PR. 983-002-034:	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode: Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04153 63	Wed, Oct 02, 1991	Letter RE: Review of Protocols
	M. Lumpkin	RE: Attached are planned protocols for two adult phase 3 studies: 1) Protocol 983-004 2) Protocol 983-008 We anticipate starting these studies in early Nov-91 and would appreciate any comments you have on the drafts.
	D. Scott	
B04153 64	Thu, Oct 10, 1991	Letter RE: Response to FDA Request for Information
	M. Lumpkin	RE: Per the request of Dr. Linda Sherman, enclosed are four copies of the case report forms for the following studies: 1) Protocol 983-004 2) Protocol 983-008 In addition, enclosed is one desk copy of the two protocols that were submitted on 02-Oct-91 (SN #63) corresponding to the above cited case report forms. Questions contact ———
	H. Holden	
B04153 65	Thu, Oct 10, 1991	Letter RE: Response to FDA Request for Information
	M. Lumpkin	RE: Reference is made to our IND 34,738 for CI-983 capsules, to your letter of 28-May-91, to our letters to the IND of 10-Jul-91, 15-Aug-91 and 19-Sep-91, and to phone discussions with Dr. Linda Sherman of your division on 07-Oct and 08-Oct-91. As requested by Dr. Sherman, we are providing brief summaries of our previously submitted responses to the questions addressed to us on page 6 (item 6) in your letter of 28-May-91 dealing with the data requested to support clinical studies in the pediatric population. The summaries are presented as follows: (Continued - see file copy)
	H. Holden	
B04153 66	Fri, Oct 18, 1991	Protocol Amendment (Change in Protocol)
		Amendment #1: PR. 983-023-000: 17-Sep-91:Adding information to study population regarding inclusion criteria and exclusion criteria.
B04153 67	Thu, Oct 24, 1991	Protocol Amendment (New Investigator)
		PR. 983-002-031:
B04153 68	Thu, Nov 07, 1991	Information Amendment (Pharmacology/Toxicology & Clinical)
		(3) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04153 69	Thu, Nov 14, 1991	Protocol Amendment (New Investigators)
		PR. 983-002-007: [redacted] PR. 983-001-009: [redacted] (Returned from active military service and will resume responsibility of principal investigator.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04153	70	Wed, Nov 27, 1991 M. Lumpkin D. Scott	PR. 983-004-001: PR. 983-004-004: PR. 983-004-011: PR. 983-004-014: PR. 983-004-021: PR. 983-004-025: PR. 983-004-028: PR. 983-004-029: PR. 983-004-031: PR. 983-004-034: PR. 983-004-038: PR. 983-004-039: PR. 983-004-050: PR. 983-004-051: RE: We have discussed this protocol with Dr. Linda Sherman, the Medical Reviewer, by telephone, and have attached an information amendment regarding issues raised and our response to them immediately after this letter. The protocol is being amended as described in this list, and these amendments will be submitted when finalized. Issue 10 concerns the inclusion of clinical response in the definition of superinfection as raised by the reviewer. We have provided the rationale for our current definition, if necessary, after coming to an agrement with the agency. We also discussed a skin and skin structure protocol with Dr. Sherman (study 983-008). (Continued - see file copy)	Protocol Amendment (New Investigators) Letter RE: Protocol Amendment (Clinical)
B04153	71	Wed, Dec 04, 1991	(2) Research Report submitted. Refer to Research Report list for RR #, date, author and title.	Information Amendment (Clinical)
B04153	72	Fri, Dec 06, 1991 M. Lumpkin D. Scott	RE: We are submitting a protocol for your review, "An Investigator-Blinded, Randomized, Comparative Multicenter Study of Cefdinir (CI-983) VS Augmentin in the Treatment of Acute Otitis Media With Effusion in Pediatric Patients (Protocol 983-011)" and would appreciate any comments that you have. This study will be conducted in Europe and is planned to start in late Jan-92. Of note at this time is section 4.3.5. The protocol will be amended to exclude patients with a serum creatinine level of 1.5, rather than, 2 times the upper limit of normal. We had agreed to make this modification in two other protocols we discussed with the Medical Reviewer, Dr. Linda Sherman. At this time also, we are formally submitting a list of issues we discussed with her by phone on a skin structure protocol (983-004). These were faxed. Questions call ——	Letter RE: Information Amendment (Clinical)

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04153	73	Thu, Dec 12, 1991		Protocol Amendments (New Investigators)
				PR. 983-004-007: PR. 983-004-013: PR. 983-004-022: PR. 983-004-023: PR. 983-004-026: PR. 983-004-037: PR. 983-004-049 PR. 983-002-033: [redacted]
B04154	74	Thu, Dec 19, 1991		Protocol Amendments (New Investigators)
				PR. 983-004-012: PR. 983-004-030: PR. 983-004-035: PR. 983-004-036: PR. 983-004-040: PR. 983-004-045: PR. 983-004-048 PR. 983-002-019: [redacted] PR. 983-016-016: [redacted]
B04154	75	Thu, Dec 19, 1991		Information Amendment (Clinical)
				(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04154	76	Thu, Dec 19, 1991		Letter RE: Information Amendment (Clinical)
				RE: Attached is a preliminary report on a recently completed study entitled, "A Single-Dose Safety, Tolerance, and Pharmacokinetic Study of CI-983 in Pediatric Patients/Subjects." This study protocol was submitted 19-Sep-91 (SN #58) and a minor amendment was submitted on 25-Sep-91 (SN #61). Data from this pilot study have been used to assess tolerance and pharmacokinetics of the pediatric suspension formulation in children, and to aid in selection doses for the pediatric phase 3 program. Questions contact———
B04154	77	Mon, Dec 30, 1991		Letter RE: General Correspondence FDA Meeting
		M. Lumpkin		RE: Attached is a copy of our letter to Ms. Sandy Childs of your division concerning the briefing package for our end-of-phase 2 meeting scheduled 13-Jan-92. Questions contact———
		D. Scott		
B04154	78	Thu, Jan 02, 1992		Protocol Amendment (New Investigators)
				PR. 983-003-035: PR. 983-003-036: PR. 983-003-037:

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/Ltr	Date	RE/Ref#	To: / From:	Report Title / Report No. / Contents / Report No.
B04154	79	Thu, Jan 02, 1992			Information Amendment (Clinical) (2) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04155	80	Thu, Jan 09, 1992			Protocol Amendment (New Investigators) PR. 983-008-002: PR. 983-008-003: PR. 983-008-004: PR. 983-008-005: PR. 983-008-006: PR. 983-008-007: PR. 983-008-008: PR. 983-008-009: PR. 983-008-010: PR. 983-008-011: PR. 983-008-012: PR. 983-008-014: PR. 983-008-016: PR. 983-008-017: PR. 983-008-018: We discussed this protocol with Dr. Linda Sherman, the Medical Reviewer, by telephone, on 06 and 08-Nov, and an information amendment regarding issues raised and our response to them was submitted on 06-Dec-91 (SN #72). This list is included again following (Tab 2). The amendments agreed to are being processed, and will be submitted when finalized. We also notify you of a clinical study to be conducted, in normal subjects, in accordance with the attached protocol 983-030-000 entitled "A Study to Evaluate Potential Pharmacokinetic Interactions Between Maalox and CI-983 (Cefdinir)" (Tab 3). PR. 983-008-019: PR. 983-008-021: PR. 983-008-022: PR. 983-008-024: PR. 983-008-025: PR. 983-008-028: PR. 983-008-034: PR. 983-008-036: PR. 983-008-049: PR. 983-008-052: PR. 983-004-009:

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04155	81	Fri, Jan 17, 1992	PR. 983-004-006: PR. 983-004-033: PR. 983-004-041: PR. 983-008-015: PR. 983-008-020: PR. 983-008-035: PR. 983-008-037: PR. 983-008-040: PR. 983-008-044: PR. 983-008-045: PR. 983-008-047: PR. 983-008-050: PR. 983-002-007: [redacted] PR. 983-004-001: [redacted]	Protocol Amendments (New Investigators)
B04155	82	Fri, Jan 24, 1992	PR. 983-004-010: PR. 983-004-024:	Protocol Amendment (New Investigators)
B04155	83	Fri, Jan 24, 1992	(2) Research Report submitted. Refer to Research Report list for RR #, date, author and title. RR 744-000444 - This report supercedes RR-Memo 724-00125 (Interim Report of Study) which was submitted on 11-Oct-90 (SN #007).	Information Amendment (Clinical)
B04155	84	Thu, Jan 30, 1992	PR. 983-004-005:	Protocol Amendment (New Investigators)
B04155	85	Mon, Feb 17, 1992	PR. 983-008-013: PR. 983-008-023: PR. 983-002-010: [redacted] PR. 983-004-051: [redacted] PR. 983-008-006: [redacted] PR. 983-008-033: [redacted]	Protocol Amendment (New Investigators)

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No.	Report Title/ Report No.
B04155	86	Tue, Feb 18, 1992		Minutes of FDA Meeting
				Date: 13-Jan-92 FDA meeting regarding the end-of-phase 2 for the oral cephalosporin cefdinir; the overheads presented at the meeting are included. This report was reissued due to a typographical error; this is its initial submission to the IND. Thus updated brochure supersedes RR-X 720-02821 which was submitted on 14-Sep-90 (SN #4).
B04155	87	Tue, Feb 18, 1992		IB Update
				Date: 24-Oct-91/07-Feb-92 RR-X 720-02983 Authors: [redacted] "Investigator's Brochure: CI-983 (Cefdinir)"
B04155	88	Tue, Feb 25, 1992		Protocol Amendment (New Investigators)
				PR. 983-029-000: Pr. 983-004-016: [redacted] PR. 983-004-019: [redacted]
B04155	89	Tue, Feb 25, 1992		Letter RE: Response to FDA Request for Information
		M. Lumpkin		RE: Dr. Barry Paull participated as principal investigator in study 983-002-011 conducted under this IND (a double-blind, randomzied comparative multicenter study of CI-983 versus trimethoprim/sulfamethoxazole in the tratment of uncomplicated urinary tract infections). In Nov-91, we received a letter from Dr. Frances Kelsey of CDER's Division of Scientific Investigations. This letter indicated that, in response to allegations of improper conduct during a clinical study with the investigational drug azelastine, Dr. Paull has agreed to no longer serve as an investigator or subinvestigator of investigational drugs. (Continued - see file copy)
		D. Scott		
B04156	90	Fri, Mar 06, 1992		Protocol Amendment (New Investigators)
				PR. 983-034-000: PR. 983-035-000: PR. 983-004-052: PR. 983-004-056: PR. 983-002-002: [redacted] PR. 983-008-021:

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No./ Contents/Report No./
B04156	91	Mon, Mar 16, 1992	Letter RE: Materials for Meeting RE: Enclosed are briefing materials for a working meeting on cefdinir scheduled for 23-Mar. Desk copies are provided for the scheduled attendees, Drs. Sherman and Albrecht, Mr. Debellas and for Dr. Harkins, who we hope may be able to attend at least the part of the meeting on subsetting logic. Three protocols are included in this package. While we welcome any comments on the study design, we hope to discuss in detail section 8.2, date interpretation. This section is similar in all three protocols, and can be found on the designated pages: (Continued - see file copy)
B04156	92	Mon, Apr 06, 1992	Follow-Up to Safety Report RE: Please refer to our IND Safety Report of 2-Apr-91 (SN #030) and the follow-up report of 25-Apr-91 (SN #036) in which a case of pseudomembranous colitis was reported. We are now submitting a second follow-up report that contains minor corrections based on a recent review. Item 12D, action taken, on the reporting form has been changed back to the original "discontinued" from "none" to reflect that cefdinir was discontinued directly in response to the symptoms of pseudomembranous colitis. The date of event onset has accordingly been corrected from 20-Mar-91 to 17-Mar-91 (items 4-6). Finally, item 12B has been updated to note that the patient recovered. The summary at the end of the form has been revised with the updated information. Questions contact———
B04156	93	Wed, Apr 08, 1992	Safety Report Patient #: None (SA) PR. AE: A 17-year old female who received cefdinir (300 MG/DAY) for an upper respiratory tract infection developed nausea, and a feeling of suffocation and unconsciousness. Her pulse was 112 and blood pressure was 106/52. She was unresponsive to auditory stimuli. She was given fluid relplacement and hydrocortisone and regained consciousness the next morning. The patient has recovered.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04156	94	Fri, Apr 10, 1992	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-010-001: PR. 983-010-008: PR. 983-010-009: PR. 983-004-027: PR. 983-010-032: PR. 983-010-053: PR. 983-008-026: Amendment #1: PR. 983-004: 27-Nov-91: We are also sumbitting addendum A for study 983-004, which will pertain to centers 983-004-001, 983-004-002, 983-004-003, 983-004-005, 983-004-006, 983-004-007, 983-004-011, 983-004-012, 983-004-014, 983-004-015, 983-004-016, 983-004-018, 983-004-020, 983-004-025, and 983-004-034. Amendment #1: PR. 983-008: 9-Jan-92: Addendum A for study 983-008 is submitted as well and will pertain to centers 983-008-001, 983-008-002, 983-008-003, 983-008-006, 983-008-009, 983-008-010, 983-008-011, 983-008-028, 983-008-029, and 983-008-031. PR. 983-004: [redacted] PR. 983-004: [redacted]
B04157	95	Thu, Apr 16, 1992	Protocol Amendment (New Investigators) PR. 983-010-002: PR. 983-010-004: PR. 983-010-011:
B04157	96	Wed, Apr 22, 1992	Protocol Amendment (New Investigators) PR. 983-038-002: PR. 983-038-019: PR. 983-038-022: PR. 983-038-005: PR. 983-038-006:

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No:
B04157	97	Wed, May 13, 1992	Protocol Amendment (New Investigators)
			PR. 983-011-003: PR. 983-011-022: PR. 983-010-003: PR. 983-010-012: PR. 983-038-001: PR. 983-038-004: PR. 983-038-006: PR. 983-038-011: PR. 983-038-015: PR. 983-038-016: PR. 983-038-017: PR. 983-038-023: Amendment #1: PR. 983-011: 13-May-92: Amendment #1 (including the rationale) for this study is also attached. We will obtain similar amendments for all active centers of the multicenter but will not submit them in order to eliminate paperwork. (Tab 1) Amendment #2: PR. 983-004: 27-Nov-91: We are attaching amendment #2 (including the rationale) for this study. We will obtain similar amendments for all active centers of the multicenter but will not submit them in order to eliminate paperwork. (Tab 2) PR. 983-004-031: [redacted] PR. 983-004-001: 29 subinvestigators have been added to work during the conduct of study 983-004-001. (See file copy for list of names) (Tab 3)
B04157	98	Tue, May 19, 1992 M. Lumpkin D. Scott	Letter RE: Protocol Amendment (New Protocol) RE: Attached are two protocols for your review, protocol 983-013 entitled, "Cefdinir Versus Cephalexin in the Treatment of Acute Uncomplicated Skin and Skin Structure Infections in Pediatric Patients," and Protocol 983-036, entitled, "An Investigator-Blinded, Randomized Comparative, Multicenter Study of Cefdinir Versus Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients." Study 983-013 is similar in design to the adult SSSI study, protocol 983-008, entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of CI-983 Versus Cephalexin in the Treatment of Skin and Skin Structure Infections," submitted on 9-Jan-92, (SN #094), although the follow-up visits are at later time points. Questions contact——

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04157	99	Fri, May 22, 1992		Protocol Amendments (New Investigators & Change in Protocol)

PR. 983-006-001:
PR. 983-006-002:
PR. 983-006-005:
PR. 983-006-010:
PR. 983-006-011:
PR. 983-006-012:
PR. 983-006-013:
PR. 983-006-014:
PR. 983-006-016:
PR. 983-006-017:
PR. 983-006-018:
PR. 983-006-021:
PR. 983-006-024:
PR. 983-006-025:
PR. 983-006-026:
PR. 983-006-027:
PR. 983-006-028:
PR. 983-006-030:
PR. 983-006-033:
PR. 983-006-034:
PR. 983-006-038:
PR. 983-011-002:
PR. 983-011-008:
PR. 983-011-009:
PR. 983-011-013:
PR. 983-011-014:
PR. 983-011-026:
PR. 983-011-028:
PR. 983-038-018:
Addendum B: 13-May-92: PR. 983-011: Addendum B for only the [redacted] centers 983-011-026 and 983-011-028 is attached.
This addendum specifies that tympanocetesis will not be allowed in any [redacted] site participating in the 983-011 study, in accordance with the recommendation of the Ethical Review Committee. This addendum allows a change to the specified age range of the patient population recruited into 983-011 study to give a minimum age of 12 months. Also the first 3 patients to be recruited must be aged 6 or over.
This addendum specifies a maximum amount of blood 5 ML, to be sampled at any one visit for the purpose of haematological and biochemical analysis.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic:
Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	IRE/ Report Title/ Report No./ Contents/Report No./
B04157	100	Fri, May 22, 1992	Letter RE: Protocol Amendment (New Protocol)
			RE: Attached are two protocols for your review, protocol 983-026 entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir VS. Amoxicillin/Clavulanic Acid in the Treatment of Community-Acquired Bacterial Pneumonia" and protocol 983-037 entitled, "A Double-Blind Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) VS. Amoxicillin with Clavulanic Acid in the Treatment of Acute Bacterial Maxillary Sinusitis (prtocol 983-037)." These studies in adults/adolescents will be conducted outside North America, but are similar in design to the North American studies currently in progress under this IND, (protocol 983-004, pneumonia - submitted 27-Nov-91,. . . . . (Continued - see file copy)
B04157	101	Tue, Jun 02, 1992	Letter RE: Response to Request for Information
		M. Lumpkin	RE: Recently we sent four protocols to the IND for review, SN #098 on 19-May-92 and SN #100 on 22-May 92. Dr. Sherman called to ask if case report forms for the protocols were available. Draft case report forms for the pediatric SSSI study (983-013) are availalbe at this time and are included in this submission. The other studies are starting later, and drafts of the case report forms are not yet available. Questions contact ———
		D. Scott	

Barcode	Ser/ Ref#	Date	RE/ To: From:	Report Title/ Report No. Contents/Report No./
B04157	102	Thu, Jun 11, 1992		Protocol Amendment (New Investigators & Change in Protocol) PR. 983-006-003: PR. 983-006-007: PR. 983-006-008: PR. 983-006-009: PR. 983-006-019: PR. 983-006-020: PR. 983-006-029: PR. 983-006-035: PR. 983-006-039: PR. 983-006-040: PR. 983-011-004: PR. 983-011-032: PR. 983-038-009: PR. 983-038-010: PR. 983-038-020: Amendment #2: PR. 983-003: 13-Nov-90: We have obtained similar amendments for all active centers of the mulltiicenter but did not submit to eliminate paperwork. PR. 983-006-024: [redacted] PR. 983-002-017: [redacted] PR. 983-004-014: [redacted] PR. 983-004-015: [redacted] PR. 983-004-040: [redacted] PR. 983-004-012: [redacted] PR. 983-004-017: [redacted] PR. 983-008-019: [redacted] PR. 983-008-028: [redacted] [redacted] PR. 983-008-032: [redacted]
B04158	103	Thu, Jun 18, 1992		Protocol Amendment (New Investigators) PR. 983-011-012: PR. 983-011-019: PR. 983-011-020: PR. 983-011-021:
B04158	104	Tue, Jun 23, 1992		Safety Report Patient #: None (YO) PR #: None AE: A 77-year old male who developed allergic vasculitis while on cefdinir therapy for the treatment of bronchitis. This event has been reported from Japan and did not occur in a study being conducted under the IND. The reporting physician considered the allergic vasculitis possibly related to study drug, and that the event prolonged hospitalizaiton. This event is considered unexpected; no prior cases of allergic vasculitis have been reported to the Waers database for cefdinir. AE: #081-0983-920006-00

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04158	105	Thu, Jun 25, 1992	Safety Report Patient: #12 (RHS) PR. 983-008-001 AE: A 22-year old male was hospitalized for bloody diarrhea which the investigator assessed as probably related to cefdinir and for appendicitis which was regarded as possibly related to cefdinir. There have been no previous reports of bloody diarrhea or of appendicitis to the Parke-Davis Safety Database. AE: #0001-0983-920008-00
B04158	106	Thu, Jun 25, 1992	Protocol Amendment (New Investigator & Change in Protocol) PR. 983-006-023: PR. 983-006-036: PR. 983-011-024: PR. 983-011-025: PR. 983-011-033: PR. 983-011-034: PR. 983-011-035: Addendum B: PR. 983-011: 22-May-92: Addendum B applies to all [redacted] centers.
B04158	107	Thu, Jun 25, 1992	Protocol Amendment (New Investigator) PR. 983-013-008: PR. 983-013-011: PR. 983-013-016:
B04158	108	Fri, Jun 26, 1992 M. Lumpkin D. Scott	Letter RE: Protocols for Review RE: Attached are two protocols for your review, protocol 983-007 entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Group A B-Hemolytic Streptococcal Pharyngitis/Tonsilitis Infections" and protocol 983-005 entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) VS Cefuroxime Axetil in the Treatment of Acute Exacerbations of Chronic Bronchitis (protocol 983-005)." Study 983-007 is a North American study in adult/adolescents that is similar in design to the international pediatric protocol, study 983-036 (sent for review on 19-May-92, SN #098). Questions contact———
B04158	109	Tue, Jul 07, 1992	Protocol Amendment (New Investigators) PR. 983-011-007: PR. 983-011-010: PR. 983-011-017: PR. 983-011-023:

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B04158	110	Thu, Jul 16, 1992	Protocol Amendment (New Investigators)
			PR. 983-031-000: PR. 983-040-000: PR. 983-041-000: PR. 983-006-006: PR. 983-011-001: PR. 983-011-005: PR. 983-013-001: PR. 983-013-005: PR. 983-013-006: PR. 983-013-009: PR. 983-013-012: PR. 983-013-013: PR. 983-013-014: PR. 983-013-017: PR. 983-013-018: PR. 983-013-020: PR. 983-004-041: [redacted] PR. 983-004-002: [redacted] PR. 983-008-001: [redacted] PR. 983-008-024: [redacted]
B04158		Thu, Jul 23, 1992	Letter from FDA: RE: [redacted]
			In a letter dated 20-Nov-92, I asked that you inform me of your intentions with regards to data verification of the studies conducted by [redacted] A copy of the letter is enclosed. As of this date, I have received no reply. Please let me know of your intentions either to [redacted]
		F. Kelsey, Ph.D., M	
B04158	111	Fri, Aug 07, 1992	Protocol Amendment (New Investigator & Change in Protocol)
		M. Lumpkin	On 22-May-92 (SN #99), we notified you of a clinical multicenter study to be conducted in accordance with protocol 983-006 entitled, "An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (600 MG QD and 300 MG BID) Versus Augmentin (500 MG TID) in the Treatment of Acute Maxillary Sinusitis for 10 Days." We are adding centers 983-006-022 and 983-006-032 to the multicenter study. Also, on 10-Apr-92 (SN #92), we notified you of a clinical multicenter study to be conducted in accordance with protocol 832-010 entitled, "An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Augmentin in the Treatment of Acute Suppurative Otitis Media With Effusion in Pediatric Patients." We are adding center 10 to this multicenter study. (Continued - see file copy)
		D. Scott	
B04159	112	Fri, Aug 07, 1992	Annual Report
		M. Lumpkin	Attached for you information and files is the annual report dated 7-Aug-92, for our cefdinir capsules and suspension IND 34,738.
		D. Scott	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode / Ref#	Ser/	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B04159		Thu, Aug 13, 1992 F. Kelsey R. Spivey	Letter RE: [redacted] As we discussed on the telephone (11-Aug-92), I am re-submitting our response to your letter of 19-Nov-91 concerning handling of data from studies conducted by [redacted] Contact------
B04159	113	Mon, Aug 17, 1992	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-006-004: [redacted] PR. 983-010-007: [redacted] PR. 983-013-007: [redacted] PR. 983-038-003: [redacted] Addendum B for PR. 983-010 Center 4 (Continued - see file copy)
B04159	114	Tue, Aug 18, 1992	Review of Protocols Attached are additional draft case report forms (CRFs) for use in OUE discussion of Cefdinir protocols with Dr. L. Sherman and C. Debellas on 2-Sep-92 (1:00 pm, Room 12-21B). The protocols submitted for review are listed below. (Continued - see file copy)
B04159	115	Tue, Aug 25, 1992	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-013-003: [redacted] Additional subinvestigators (Continued - see file copy)
B04159	116	Tue, Sep 01, 1992	Information Amendment (Clinical) For your information, we are submitting a report of diarrhea with overdosage recently observed in one of the cefdinir otitis media studies (983-011) a nine-year old female developed diarrhea after receiving three times the prescribed dose of cefdinir on four separate occasions. Diarrhea is an expected event with cefdinir, and did not result in hospitalization. Although the event was reported as an overdose, it is not clear that three times is the correct dose constitutes a true overdose for a cephalosporin-type agent. We are, however, submitting the attached event data for your information. Contact------
B04159	117	Wed, Sep 02, 1992 M. Lumpkin D. Scott	Protocol Amendment (New Investigators) We have been notified of the addition of several subinvestigators to several study centers. (Continued - see file copy)
B04159	118	Mon, Sep 14, 1992	Protocol Amendment (New Investigators) PR. 983-038-007: [redacted]

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode / Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04159	119	Tue, Sep 22, 1992	Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-007-006: [redacted] PR. 983-007-009: [redacted] PR. 983-007-011: [redacted] PR. 983-007-022: [redacted] PR. 983-007-025: [redacted] Addendum A for PR. 983-007: Provides for pharmacokinetic sampling and analysis at selected sites. Contact———
B04159	120	Wed, Sep 30, 1992	Protocol Amendment (New Investigators)
			PR. 983-038-024: [redacted]
B04159	121	Mon, Oct 05, 1992	Protocol Amendment (New Investigators)
			PR. 983-007-003: [redacted] PR. 983-007-005: [redacted] PR. 983-007-014: [redacted] PR. 983-007-017: [redacted] PR. 983-007-023: [redacted]
B04159	122	Fri, Oct 09, 1992	IND Safety Report: Initial Written Report
			We are submitting IND safety reports on two events that were reported to us from Japan; neither event occurred in a study being conducted under the IND. Event number 14974 is an 18-year old male who reported blood diarrhea and melena. Event number 15090 is a case of a 25-year old male who had a clonoscopy and was diagnosed with hemorrhagic colitis; he was also taking diclofenac. The physician believed the event was probably related to the use of cefdinir and diclofenac (possible interaction). Both patients have recovered. No similar events have been previously reported to our worldwide adverse event reporting system. Contact———

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No./ Contents/Report No./
B04159	123	Mon, Oct 19, 1992	Protocol Amendments (New Protocol/New Investigators/Change in Protocol) PR. 983-005-005: [redacted] PR. 983-005-006: [redacted] PR. 983-005-007: [redacted] PR. 983-005-008: [redacted] PR. 983-005-009: [redacted] PR. 983-005-010: [redacted] PR. 983-005-017: [redacted] PR. 983-005-019: [redacted] PR. 983-005-020: [redacted] PR. 983-004-058: [redacted] PR. 983-007-002: [redacted] PR. 983-007-016: [redacted] PR. 983-007-0021: [redacted] PR. 983-011-036: [redacted] Addendum A for PR. 983-007-002, 983-007-013, 983-007-016, 983-007-017, 983-007-023, and 983-007-025 Addendum B for PR. 983-008-005, 983-008-006, 983-008-010, 983-008-011, 983-008-015, 983-008-019, 983-008-021, 983-008-023, 983-008-024, and 983-008-052. PR. 983-004-001: [redacted] (Continued - see file copy)
B04159	124	Mon, Oct 19, 1992	IND Safety Report: Initial Written/Follow-Up Report We are submitting an IND safety report on an event reported to us from Japan; it did not occur in a study being conducted under the IND. This event, #15611, is a case of a 52-year old female who was hospitalized with the diagnosis of drug-induced pneumonia and nephropathy. The lymphocyte stimulation test was positive for the study medication and for the concomitant medications ibuprofen and streptokinase/streptodomae. The patient has recovered. Nephropathy has not been reported previously to our worldwide adverse event reporting system. A listing of two reported pnemonias is attached. We are also submitting follow-up information on a previously reported event (event 13368, submitted 25-Jun-92, SN #105). The events described therein were bloody diarrhea and appendicitis. Further information regarding the bloody diarrhea had led to A modification of the classification from bloody (Continued - see file copy)

Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No:
B04160	125	Wed, Oct 21, 1992 M. Lumpkin D. Scott	Protocol Amendment (New Protocol & New Investigators) New Protocol 983-026, New Center 983-026-009: P.J. Arens, MD PR. 983-026-012: [redacted] PR. 983-026-013: [redacted] PR. 983-026-014: [redacted] PR. 983-026-015: [redacted] PR. 983-026-016: [redacted] PR. 983-026-019: [redacted] PR. 983-007-001: [redacted] PR. 983-007-004: [redacted] PR. 983-007-007: [redacted] PR. 983-007-010: [redacted] PR. 983-007-020: [redacted] PR. 983-006-015: [redacted] Contact——	
B04160	126	Wed, Oct 28, 1992	Protocol Amendment (New Investigators) PR. 983-007-012: [redacted] PR. 983-007-019: [redacted] PR. 983-007-024: [redacted]	
B04160	127	Thu, Nov 05, 1992	Protocol Amendment (New Investigators) PR. 983-005-011: [redacted] PR. 983-005-014: [redacted] PR. 983-026-010: [redacted] PR. 983-038-012: [redacted]	
B04160	128	Mon, Nov 09, 1992	Information Amendment (Pharmacology/Toxicology & Clinical) (6) Research Report submitted. Refer to Research Report list for RR #, date, author and title. Revisions for RR 745-01572 and 745-01573. (Continued - see file copy)	
B04160	129	Thu, Nov 12, 1992 M. Lumpkin D. Scott	Protocol Amendment (New Protocol & Change in Protocol) New Protocol 983-036 entitled, An Investigator-Blinded, Randomized, Comparative, Multicentre Study of Cefdinir Versus Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Paediatric Patients. New Center 983-036-003: E. [redacted] Addendum A for center 3: Increases the minimum age of entry to 12 months. Also, the first three patients to be recruited must be age 6 or over. The addendum also specifies a maximum amount of blood, 5ML, to be sampled at any one visit for hematological and biochemical analysis. Contact——	

IND/NDA/DMF#:	34,738	IND	Doc Type: FDA CORRESPONDENCE
			SubType: IND
CI#	983	Sub Date:	4/30/90
Generic		Appr Date:	
Product Name:	Cefdinir		

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B04160	130	Thu, Nov 19, 1992	Protocol Amendment (New Protocol/New Investigator/Change in Protocol) PR. 983-037-001: [redacted] PR. 983-037-003: [redacted] PR. 983-037-004: [redacted] PR. 983-037-005: [redacted] PR. 983-037-006: [redacted] PR. 983-037-010: [redacted] PR. 983-037-011: [redacted] PR. 983-037-012: [redacted] PR. 983-037-013: [redacted] PR. 983-037-014: [redacted] Addendum A for center 1: Increases the minimum age of entry to 18 at all 983-037 investigational sites in Finland. This addendum is in accordance with local country requirements for the clinical investigation of new drugs and changes section 4.2.2.(page 8). (Continued - see file copy)
B04161	131	Tue, Nov 24, 1992	Protocol Amendment (New Investigator) PR. 983-019-001: [redacted] PR. 983-011-031: [redacted] PR. 983-007-015: [redacted] PR. 983-036-008: [redacted]

Barcode / Ser/ Ref# | Date | To: | From: | RE/ Report Title/ Report No./ Contents/Report No./

B04161	132	Thu, Dec 03, 1992	Protocol Amendment (New Investigators & Change in Protocol)

PR. 983-004-060: [redacted]
PR. 983-004-025: New IRB address:
Old Address: Institutional Review Board, VAMC, 4801 Linwood Blvd., Kansas City, MO 64128
New Address: [redacted]
PR. 983-005-001: [redacted]
PR. 983-005-002: [redacted]
PR. 983-005-003: [redacted]
PR. 983-005-004: [redacted]
PR. 983-036-002: [redacted]
PR. 983-036-007: [redacted]
PR. 983-036-009: [redacted]
PR. 983-036-016: [redacted]
PR. 983-037-002: [redacted]
PR. 983-037-015: [redacted]
PR. 983-019-002: [redacted]
PR. 983-004-016: [redacted]y: Center submitted on 27-Nov-91 (SN # 0)
PR. 983-038-011: [redacted]Center submitted on 13-May-92 (SN #97)
PR. 983-013-005: [redacted]
PR. 983-013-006: J[redacted]rs submitted on 16-Jul-92 (SN #110)
PR. 983-010-006: [redacted] submitted on 22-Apr-92 (SN #96)
PR. 983-008-006: [redacted]
PR. 983-008-052: [redacted] Centers submitted on 9-Jan-92 (SN #80)
PR. 983-006-010: [redacted]
PR. 983-006-018: [redacted]
PR. 983-006-030: [redacted]. Centers submitted on 22-May-92 (SN #99)

B04161	133	Tue, Dec 15, 1992	IND Safety Report: Initial Written
		M. Lumpkin	

We are submitting a safety report on a case of hepatic dysfunction and jaundice reported from post-marketing surveillance in Japan; the event did not occur in a study being conducted under the IND.
Cefdinir was begun prophylactically after an appendectomy in a 28-year-old male whose liver enzymes were elevated prior to receiving drug. Cefdinir was continued for eight days; liver enzymes peaked 7-8 weeks after therapy. There was a positive cefdiinir lymphocyte stimulation test. The reporting physician considered a possible causal relationship between the event and the drug. The PD medical reviewer considered the relationship unlikely based upon the elevation pattern and experience with other beta lactum agents. All investigators are being notified of this event. . .
(Continued - see file copy)

D. Scott

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04161	134	Wed, Dec 16, 1992		Protocol Amendment (New Investigator)
			PR. 983-042-000:	
B04161	135	Tue, Dec 22, 1992		Protocol Amendments (New Investigators & Change in Protocol)
			PR. 983-011-016: PR. 983-006-041: Addendum A: PR. 983-006-013: PR. 983-006-026:PR. 983-006-033: 26-Mar-92: Provides for the collection of a 4-hour post-morning dose sample of blood for further pharmacokinetic analysis. PR. 983-005-013: PR. 983-026-002: PR. 983-026-003: PR. 983-026-018: PR. 983-037-007: PR. 983-037-009: PR. 983-019-004: PR. 983-004-064: PR. 983-004-065:	
B04161	136	Fri, Jan 08, 1993		Protocol Amendments (New Investigators & Change in Protocol)
			PR. 983-036-011: PR. 983-036-014: PR. 983-036-015: PR. 983-004-001: [redacted] PR. 983-007-005: [redacted] PR. 983-038-017: [redacted] New address: Institutional Review Board - see file copy PR. 983-007-024: Dropped as subinvestigator: D. McLeod,RN	
B04161	137	Mon, Jan 11, 1993		Safety Report
			Patient: # /YW PR. 983 AE: Thrombocytopenia AE: #18365 Patient: # /AS PR. 983 AE: Facial edema and larynogopharyngael edema AE: #18788 Patient: # /MO PR. 983 AE: Phabdomyolysis AE: #19153	

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04161	138	Fri, Jan 29, 1993	Protocol Amendment (New Investigators) PR. 983-007-022: [redacted] PR. 983-007-001: [redacted] PR. 983-010-005: [redacted] PR. 983-006-010 [redacted] PR. 983-006-033: [redacted] (Continued - see file copy)
B04161	139	Fri, Feb 05, 1993	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-004-059: [redacted] PR. 983-004-062: [redacted] PR. 983-010-013: [redacted] PR. 983-005-023: [redacted] PR. 983-026-008: [redacted] PR. 983-026-020: [redacted] PR. 983-026-021: [redacted] PR. 983-026-022: [redacted] PR. 983-036-013 [redacted] PR. 983-036-019: [redacted] PR. 983-036-020: [redacted] We have also been notified of the addition of subinvestigators to four study centers. (Continued - see file copy)
B04161	140	Mon, Feb 08, 1993	IND Safety Report/Initial Written Report Patient: # (KM) PR.: None AE: # None (Waers event # 20230) Possibly study drug related. AE: Idiopathic interstitial pneumonia, patient was hospitalized.
B04161	141	Wed, Feb 17, 1993	Information Amendment (Clinical) We faxed Dr. L. Sherman a proposed change in our sinusitis program for cefdinir. We will be discussing it on 17-Feb-93 at 1:00 pm, at the USP, with Dr. Sherman, Mr. Dedellas, and Dr. Ralph Harkins. We are sending a copy of the proposal now so that it may be part of our official IND file. Contact------- (see file copy)

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04161	142	Fri, Feb 19, 1993		Protocol Amendment (New Protocol/New Investigators/Change in Protocol)

New Protocol 983-043 entitled, A Study to Determine the Effect of Time of Administration of a Therapeutic Iron Dose on Cefdinir Absorption. A. Sedman, MD/E.
[redacted]
PR. 983-004-063: [redacted]
PR. 983-011-037: [redacted]
PR. 983-007-008: [redacted]
Addendum B for center 8 in study 983-007 which some rewording requested by the Health Protection Bureau in Canada.
PR. 983-005-016: [redacted]
PR. 983-005-022: [redacted]
PR. 983-026-001: [redacted]
PR. 983-036-021: [redacted]
PR. 983-037-008: [redacted]

B04161	143	Mon, Feb 22, 1993		IND Safety Report: Initial Written Report

Patient : # (HM)
PR.: Foreign
Event: #20631
[redacted]
Possibly related to cefdinir
The events did not occur in studies being conducted under the IND; they were reported from post-marketing experience in Japan, [redacted]

B04161	144	Fri, Feb 26, 1993		Protocol Amendments: New Investigators)

Added new centers:
PR. 983-004-067:
PR. 983-011-018:
PR. 983-006-043:
PR. 983-026-023:
PR. 983-036-024:
PR. 983-006-011: [redacted]
PR. 983-006-030: [redacted]
May-92 (SN # 099)
PR. 983-038-009: [redacted] Center submitted on 11-Jun-92 (SN #102)
PR. 983-007-017: [redacted] Center submitted on 6-Oct-92 (SN #121)
PR. 983-007-012: [redacted] ter submitted on 28-Oct-92 (SN #126)
Contact------

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04161	145	Fri, Mar 05, 1993		Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-006-046: [redacted] PR. 983-036-031: [redacted] PR. 983-037-018: [redacted] We have been notified of a change of address for Principal Investigator [redacted] (PR. 983-004-029) (27-Nov-92; SN #70). Old: Simon-Williamson Clinic, P.C., 833 Princeton Avenue, S.W., Birmingham, AL 35211. New: [redacted]	
B04161	146	Fri, Mar 05, 1993		Information Amendment (Clinical)
			(3) Research Report submitted. Refer to Research Report list for RR #, date, author and title. RR 745-01748 - Page (I) Revision - Lot Number	
B05886	147	Fri, Mar 19, 1993		Protocol Amendments (New Investigator & Change in Protocol)
			Add Centers: PR. 983-004-061: PR. 983-004-066: New Subinvestigators: [redacted] submitted on 12-Dec-91 (SN #073)	
B05886	148	Fri, Apr 02, 1993		Protocol Amendment (New Investigators)
			PR. 983-036-017: [redacted]	
B05886	149	Mon, Apr 05, 1993		Closing FDA Master File 535
		M. Lumpkin	We are in the process of discontinuing our FDA Master File 535 which was initiated on 9-Apr-63 in our FDA-MIS file, SN #5. Reference is made to our second page of standard letters for protocol amendments: new protocol, in which we state, "filed in section 5 of MF 535 for Drs. Dawkins, and Vassos." This statement appears under the heading, "Investigator Qualifications." These investigators have participated in the following studies filed under IND #34,738. (Continued - see file copy)	
		D. Scott		
B05886	150	Thu, Apr 08, 1993		Protocol Amendment (New Investigators)
			PR. 983-006-048: [redacted]	

Best Available Copy

IND/NDA/DMF#:	34,738	IND	Doc Type:	FDA CORRESPONDENCE	11/3/97	Page 38
			SubType:	IND		
CI#:	983		Sub Date:	4/30/90		
Generic:			Appr Date:			
Product Name:	Cefdinir					

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B05886	151	Tue, Apr 27, 1993	Protocol Amendment (New Protocol & Change in Protocol)
		M. Lumpkin	New Protocol 983-051 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir Versus Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients. New Centers: 983-051-002: H. [redacted] 983-051-003[redacted] 983-051-005:[redacted] 983-051-007:[redacted]MD, 983-051-011: [redacted] Regarding Protocol 983-004: Amendment #3 which notes that patients requiring therapy with magnesium- or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before and two hours after study drug dosing. We will obtain similar amendments for all remaining active centers but will not submit them in order to eliminate paperwork. PR. 983-038: Addendum A for 983-038-016, which was created to determine sputum concentrations of cefdinir after dosing in patients with secondary bacterial infections of acute bronchitis. PR. 983-006: Amendment #1 which notes that patients requiring therapy with magnesium- or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before and two hours after study drug dosing. We .... paperwork. PR. 983-013: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. PR. 983-005: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. PR. 983-026: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. PR. 983-037: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. [redacted], MD will assume Principal Investigator responsibilities, [redacted] for studies 983-004-012, 983-013-018, 983-006-026 and 983-038-016.
		D. Scott	

SubType: IND

CI#: 983 Sub Date: 4/30/90

Generic: Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B05886	152	Wed, May 19, 1993	Protocol Amendments (New Protocol & New Investigators)
			New Protocol 983-024 entitled, A Study of Cefdinir (CI-983) Penetration into Tonsil Tissue in Patients Undergoing Elective Tonsillectomy. PR. 983-011-023: PR. 983-011-038: PR. 983-026-031: PR. 983-037-017: PR. 983-051-001: PR. 983-051-004: PR. 983-051-008: PR. 983-051-009: PR. 983-051-010: New Sub-Investigators: PR. 983-013-015: PR. 983-013-019: PR. 983-006-022: PR. 983-007-025: PR. 983-006-041: PR. 983-004-063: PR. 983-004-067:
B05886	153	Wed, May 26, 1993	Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-051-014: Amendment #1: PR. 983-042-000: 16-Mar-93: Amendment 1 notes a change in time of tissue and blood collection for cefdinir assay, and an addition of 4 patients.
B05886	154	Wed, Jun 09, 1993	IND Safety Report: Initial Written Report
			Patient: # none (RY) PR. Japan where drug is marketed by Fujisawa AE: [redacted] sulpyrine, a sulfa drug known to be associated with TEN. Possibly related to cefdinir.
B05886	155	Tue, Jun 15, 1993	Safety Report
			Patient: # none (OT) PR. [redacted]

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B05886	156	Fri, Jun 18, 1993	Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-007-018: [redacted] Amendment #1 for 983-007 which notes that cefdinir has been shown to interact with Maalox. Patients requiring therapy with magnesium- or aluminum-containing antiacid therapy for two hours before and two hours after study drug dosing. We will . . . paperwork. Addendum B for PR. 983-007-018 which notes minor revisions requested by the Canadian Health Protection Bureau (HPB). PR. 983-026-024: [redacted] PR. 983-026-026: [redacted] PR. 983-026-027: [redacted] PR. 983-026-028: [redacted] Addenda A, B, &C for PR. 983-026: A - Provides for exclusion of patients with acute, or history of, pseudomembraneous colitis. (Continued - see file copy)
B05886	157	Mon, Jun 28, 1993	Information Amendment (Pharmacology/Toxicology)
			(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B06151	158	Wed, Jul 14, 1993	Information Amendment (CMC)
	158		RR-Reg 730-01959 - Updating the Chemistry, Manufacturing and Controls for the drug substance for cefdinir capsules and suspension. In an earlier amendment (SN #33, 18-Apr-91), we updated the IND specifications and test methods for accepting the new drug substance from the manufacturer, Fujisawa Pharmaceutical Company. These specifications were established based on the limited experience of 5 early lots. We are updating the specifications and test method to reflect current experience with the drug substance as the development of this compound progresses further. We wish to change the purity of the drug substance from 98.0 to 102.0% to 97.0 to 102.0% and the limit for the impurities PD 138339 and PD 151833 from 0.5% each to not more than 0.6% each. The specification of 98.0 to 102.0% for drug substance purity was supported by our . . . (Continued - see file copy)
B06151	159	Mon, Jul 19, 1993	IND Safety Report: Initial Written Report
			Patient: MK PR. None - Japan where drug marketed AE: #081-0983-930006-00 AE: [redacted]

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	160	Mon, Jul 26, 1993		Protocol Amendment (New Investigator & Change in Protocol)

PR. 983-051-015: [redacted]
PR. 983-010-006: Addendum B which requires that applicable centers enroll a maximum of 30 patients without baseline tympanocentesis. Subsequently, all guardians must consent to this procedure for the patient to be entered into the study.
Also several subinvestigators have been added to various studies.
(Continued - see file copy)

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	161	Tue, Aug 03, 1993		IND Safety Report: Follow-Up Report

Initial Report Submitted: 19-Jul-93 (SN #159)
PT: (MK)
PR. Marketed Drug in Japan
AE: #081-0983-930006-01
At that time, t[redacted]f [redacted] We have now learned that three concomitant drugs, flomoxef sodium, cefaclor, and sulfamethoxazole,trimethoprim were considered suspect by the reporter. Also, the course of events is now listed as impaired bone marrow, leukopenia, thrombocytopenia, DIC, sepsis, cerebral hemmorrhage, cardiac failure, and death.
(Continued - see file copy)

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	162	Mon, Aug 09, 1993		Annual Report

Attached for your information and files is our annual report.
Dated: 6-Aug-93
IND: 45,738, cedfinir (CI-983) capsules and suspension

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	163	Thu, Aug 12, 1993		Protocol Amendment (New Investigators)

PR. 983-006-049: [redacted]
PR. 983-026-035: [redacted]
PR. 983-026-038: [redacted]
PR. 983-026-045: [redacted]
PR. 983-037-020: [redacted]

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	164	Tue, Aug 24, 1993		Safety Report

Patient: # (IT)
Pr. 983
AE: #081-0983-930008-00
AE: Thrombocytopenia, disseminated intravascular coagulation (DIC), and eruption.

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B06151	165	Wed, Aug 25, 1993 M. Lumpkin D. Scott	Meeting Request for CANADA We are requesting a meeting to discuss our planned CANDA for cefdinir, which is scheduled for 1995. Our major goal is to provide a useful means for the medical reviewer to query and create analyses from the database. For the agenda, we suggest that we describe our planned NDA, the minimum functionality expected from our CANDA, and the features we hope to be able to provide. We would then like to hear from the Agency what aspects of CANDA's you have found most useful in reviewing NDA's. We plan to bring six attendees, if possible, from the areas of Regulatory Affairs, Clinical Research, Biometrics, and Research Information Systems. We would hope that from the FDA at least the following could attend: [redacted] Good meeting days for us would be October 4, 5, 7, 8, or 11. We will provide a briefing package two weeks before the meeting.
B06151	166	Thu, Aug 26, 1993 M. Lumpkin D. Scott	Protocol Amendment: New Protocol New Protocol: 983-048-000 entitled, A Pharmacokinetic Study of Cefdinir Concentrations in Ear Fluid and Plasma After Oral Administration of 7 mg/kg BID or 14 mg/kg QD to Pediatric Patients with Acute Suppurative Otitis Media Princ. Invest: [redacted]
B06151	167	Mon, Sep 13, 1993 M. Lumpkin D. Scott	Protocol Amendment: New Invest/Change in Protocol New Invest: 983-026-032, 983-026-036, 983-026-037, 983-026-039, 983-026-048, 983-026-049 Princ: Invest: [redacted] Coinvest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest [redacted] Princ. Invest: [redacted] 983-026: Amendment 2 New Invest: 983-005-024 Princ. Invest. [redacted] 983-005: Addendum B, C. D

Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	168	Thu, Sep 16, 1993 M. Lumpkin D. Scott	We are submitting an information amendment on a case [redacted] (Adverse Event No. 081-0983-930015-00). The event did not occur in a study being conducted under the IND; it was reported from post-marketing experience by [redacted]	Information Amendment: Clinical
B06151	169	Thu, Sep 23, 1993 M. Lumpkin D. Scott	We have additional information on a report [redacted] dverse Event No. 081-0983-930015-00) that we submitted earlier on September 16, 1993 (Serial No. 168), as a clinical information amendment. Follow-up information obtained by Fujisawa Pharmaceutical Co. about this 64-year-old female who was hospitalized for acute renal failure 9 days after completing cefdinir for bronchitis indicates that the reporting physician now considers the event unlikely related to cefdinir. This change in causality is based on a kidney biopsy that showed changes in glomeruli, not of tubules. Tubules are susceptible to the renal toxicity of -lactam antibiotics. A revised reporting form is attached. As the [redacted] is now considered unlikely to be related to cefdinir by the reporting physicians from Japan and the Parke-Davis medical reviewer, the event will be reported as an IND safety report.	Information Amendment: Clinical
B06352	170	Wed, Sep 29, 1993 M. Lumpkin D. Scott	New Investigator: 983-005-025 Protocol Filed: 10/19/92 (Ser. No. 123) Princ. Invest: [redacted] New Investigator: 983-026-029, 983-026-040, 983-026-042, 983-026-043, 983-026-044, 983-026-052 Protocol Filed: 10/21/92 (Ser. No. 125) Princ. Invest: [redacted] Princ. Invest: [redacted] Coinvestigator: [redacted] Princ. Invest: [redacted] Coinvestigator: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Coinvestigator: [redacted] Princ. Invest: [redacted]	Protocol Amendment: New Investigator

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ * Report Title/ Report No. Contents/Report No./ *
B06352	171	Wed, Oct 06, 1993 M. Lumpkin D. Scott	Information Amendment: Clinical Please refer to our fax of September 20, 1993 to Carmen Debellas of your Division, which contained a question on analysis of our sinusitis studies. We are now submitting this officially to the IND file, along with the results of a discussion we held on this issue with Drs. Ralph Harkins and Linda Sherman on September 23, 1993, at the Anti-Infective Advisory Committee Meeting. The questions were on the preferred placement for analysis of two patients who were not scheduled to receive antral punctures (taps), but who inadvertently received randomization numbers reserved for tap patients. Drs. Harkins and Sherman indicated that for the clinical evaluable patient analysis the patients should be placed with the clinical group to which they belong, i.e., the non-tap group. (Dr. Harkins said that even patients who are tapped but from whom no organism is isolated are placed in this group for analysis.) For the Intent-to-Treat meta-analysis of the sinusitis studies, the patients should be analyzed as they were randomized, i.e., in the tap group. Our analyses will follow this recommendation. If there are any further questions or comments please contact me at 313/996-1819 or FAX 313/996-7890.
B06352	172	Mon, Oct 11, 1993 M. Lumpkin D. Scott	Protocol Amendments: New Protocol New Protocol 983-049,, The Bronchoalveolar Distribution of Single-Doses of Cefdinir (CI-983) in Subjects Undergoing Diagnostic Bronchoscopy. New Protocol: 983-052,, A Single-Dose Study of Cefdinir (CI-983) Pharmacokinetics in Healthy Lactating Women and Evaluation of Cefdinir Concentrations in Breast Milk. New Protocol: 983-053 A Study of Cefdinir (CI-983) Penetration Into Sinus Tissue and Sinus Fluid in Patients Undergoing Elective Surgery on the Maxillary and Ethmoid Sinuses.

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06352	173	Fri, Oct 15, 1993 M. Lumpkin D.Scott	Attached is a briefing package for our Cefdinir CANDA meeting on November 1, 1993, at 10:00 a.m., in Room 12B-21, at the Parklawn Building. We understand that the following persons will attend from FDA: Renata Albrecht, M.D. - Supervisory Medical Officer Carmen Debellas - Project Manager Ralph Harkins, Ph.D. - Biometrics Linda Sherman, M.D. - Medical Officer Attending from Parke-Davis will be the following: [redacted] - System Specialist, Regulatory Affairs [redacted] - Manager, Anti-Infectives, Clinical Research [redacted] - Manager, Regulatory Affairs [redacted] - System Analyst, Scientific Information Engineering Drusilla Scott, Ph.D. - Director, Regulatory Affairs [redacted] - Sr. Director, Anti-Infectives, Clinical Research [redacted] - Associate Director, Biometrics	Pre-Meeting Briefing Package
B06352	174	Fri, Nov 05, 1993 M. Lumpkin D. Scott	New Investigator: 983-005-026 and 983-005-027 - Protocol Orig. Filed 10/19/92 (Ser. No. 123) Princ. Invest: [redacted] Princ. Invest: [redacted] 983-005-027 - ADDENDUM E 983-005-026 added to ADDENDUM E - Orig. Filed 9/13/93 (Ser. No. 167) New Investigator: 983-026-033 Princ. Invest: [redacted] New Invest: 983-051-012 Princ. Invest: [redacted] 983-051 - Revised pages of protocol were filed 983-051-012 - ADDENDUM A 983-036 - AMENDMENT 2 - Protocol filed 11/12/92 (Ser. No. 129) Principal Investigator addresses updated for 983-007-010, 983-006-041, 983-051-003. Several subinvestigators added to studies.	Protocol Amendment:s: New Investigator/Change in Protocol

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06352	175	Mon, Nov 08, 1993 M. Lumpkin P. Chen	Reference is made to our IND 34,738 for Cefdinir Capsules. In an early amendment (Serial No.033; Research Report No. REG 956-00111), submitted on April 18, 1991, the formulation number for 100 mg capsules in page 4 was identified as formulation 22. The correct number should be formulation 32. We have provided a replacement as Attachment 1. Please replace page 4 in the Research Report No. REG 956-00111 with the attached page. In another information amendment (Serial No. 054), submitted to you on August 21, 1991, we updated the chemistry, manufacturing and controls information to include the 300 mg capsules strength (formulation 24). For comparative clinical studies, the 300 mg capsules (size No.1) have to be encapsulated into gray/gray size No.0 capsules in order to match the encapsulated positive controls for blinding purpose. During the encapsulation operation, about 50 mg microcrystalline cellulose, NF are added to fill the empty space in the size No.0 capsules. Research Report No. RR-REG 956-00160 (Attachment 2) provides the formulation and manufacturing information for the gray/gray size 0 Cefdinir 300 mg capsules. Appendix 2 of the report presents the comparative dissolution results between the size No. 1 and encapsulated size 0 Cefdinir 300 mg capsules. The results demonstrate that an addition of about 50 mg microcrystalline cellulose has no effect on the dissolution. The specification and analytical method remain unchanged. Appendix 1 of the same report provides the stability data for the encapsulated size 0 Cefdinir 300 mg capsules. The data indicates that encapsulated capsules are stable. We will monitor the stability for the planned duration of the proposed clinical studies. We would appreciate your adding this amendment to our Cefdinir IND file.	Protocol Amendment: Change in Protocol
B06475	176	Tue, Nov 16, 1993 M. Lumpkin D. Scott	On November 1, 1993 we met with members of your division to discuss the upcoming NDA/CANDA for cefdinir. At that meeting, Dr. Linda Sherman, the medical reviewer, agreed to review a draft clinical report to evaluate whether some of the appendices containing clinical summary tables and data listings should be eliminated from future reports. A draft report of a urinary tract study, 983-002, is enclosed for evaluation, and a desk copy with tabs is included for Dr. Sherman. Some of the statistical appendices are not yet available, but these do not constitute the bulk of the appendices and will be available in the final report for comment.	Information Amendment: Clinical

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B06492	177	Tue, Nov 23, 1993 M. Lumpkin D. Scott	Protocol Amendments: New Investigator New Investigator: 983-004-068 Princ. Invest: [redacted] New Investigator: 983-026-046 and 983-026-047 Princ. Invest: [redacted] Princ. Invest: [redacted]
B06492	178	Wed, Nov 24, 1993 M. Lumpkin D. Scott	General Correpondence: Meeting Minutes Reference is made to our IND 34,738 for Cefdinir Capsules and Suspension. On November 1, 1993 we held an initial meeting to discuss the functionality of the cefdinir CANDA with members of your division. Our minutes of that meeting are attached. We would appreciate any comments on them, and when available, a copy of the Agency minutes.
B06492	179	Wed, Dec 01, 1993 M. Lumpkin D. Scott	IND Safety Report: Initial Written Report We are submitting an initial IND Safety Report on cefdinir (Adverse Event No. 081-0983-930022-00). The events being reported are peptic ulcer and eruption. They did not occur in an IND study; they were reported from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This is a case of an 11-year-old male with an upper respiratory infection who concurrently received tolmetin and cefdinir. He developed an eruption (erythema exudative multiforme) and a gastroscopy-confirmed peptic ulcer. The physician in Japan considered both events probably related to cefdinir. The Parke-Davis Medical Reviewer considered the rash possibly related to cefdinir and the peptic ulcer likely related to tolmetin rather than cefdinir. There have been no prior similar reports of peptic ulcer to our Worldwide Adverse Events Reporting System (WAERS) dababase. Erythema exudative multiforme is labelled. However, since the reporting physician considered the events probably related to cefdinir, we are submitting the information as an IND safety report.

Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06492	180	Thu, Dec 02, 1993 M. Lumpkin D. Scott	Information Amendment: Clinical Correction to Previous Amendment	Please refer to Serial Nos. 168 and 169 for IND 34,738, submitted September 16 and 23, 1993 respectively. In these information amendments, we provided available data on a case of acute renal failure reported from post-marketing experience in Japan. In Serial No. 168, we noted that insufficient information was available to determine the accuracy of the diagnosis [redacted]nd the relationship to cefdinir. Shortly thereafter we obtained additional information on the basis of a [redacted] that led both the reporting Japanese physician and the Parke-Davis medical reviewer to conclude that the event was unlikely to be related to cefdinir, and reported this in Serial No. 169. Because of this lack of a reasonable association with the use of the drug, we intended to state in Serial No. 169 that the event would not be submitted as an IND safety report. The word "not" was inadvertently omitted from the relevant paragraph. The corrected paragraph is shown below, and a copy of the Serial No. 169 letter is attached for reference: "As the [redacted] is now considered unlikely to be related to cefdinir by the reporting physician from Japan and the Parke-Davis medical reviewer, the event will not be reported as an IND safety report."
B06492	181	Thu, Dec 09, 1993 M. Lumpkin D. Scott	Protocol Amendments: New Investigator	New Investigator: 983-005-029 and 983-005-030 Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-026-050 and 983-026-055 Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-037-021 and 983-037-022 Princ. Invest: [redacted] Co-Invest: [redacted]
B06492	182	Tue, Dec 14, 1993 M. Lumpkin P. Chen	Information Amendment: Chemistry, Manufacturing and Controls	Attached is an information amendment to our IND 34,738, updating the stability data for the Manufacturing and Controls for Cefdinir 300 and 100 mg Capsules. Formulation No. 32 is the 100 mg capsule, whereas formulation 24 is the 300 mg capsule. In addition, we have packaged the 100 mg capsule in a blister package. The specifications for the blister package components are also provided in the attachment.
B06522	183	Tue, Dec 14, 1993 M. Lumpkin D. Scott	Information Amendments: Clinical	(2) Research Reports submitted See Research Report list for RR #, author, date and title.

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B06522	184	Fri, Jan 14, 1994 M. Lumpkin D. Scott	Information Amendment: Clinical (1) Research Report Submitted See Research Report List for RR#, author, date and title.
B06720	185	Wed, Jan 19, 1994 M. Lumpkin D. Scott	Protocol Amendments: New Investigators/Change in Protocol New Investigator: 983-004-069, 983-004-070, 983-004-071, 983-004-072, 983-004-073 Orig. Filed 11/27/91 (Ser. No. 070) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest:: [redacted] Princ. INvest: [redacted] New Investigator: 983-006-050 Orig. Filed 5/22/92 (Ser. No. 099) Princ. Invest: [redacted] New Investigator: 983-026-051, 983-026-053, 983-026-054 Orig. Filed 10/21/92 (Ser. No. 125) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-019-006 Orig. Filed 11/24/92 (Ser. No. 131) Princ. Invest: [redacted] 983-048-000: [redacted]. replacing James A. Hedrick, M.D. as principle investigator. Added several subinvestigators Change of address for 983-004-064 [redacted]
B06720	186	Thu, Jan 27, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Investigator New Investigator: 983-004-074 Princ. Invest: [redacted]

SubType: IND

Cl#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B06720	187	Mon, Jan 31, 1994 M. Lumpkin	IND Safety Report: Initial Written Report In accordance with 21 CFR 312.32 (c), we are submitting an initial IND Safety Report on cefdinir (Adverse Event No. 081-0983-940016-00). The events being reported are shock and asthmatic attack. They did not occur in an IND study, rather from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This is a case of a one-year-old male with allergic bronchitis who started cefdinir when his cough became increasingly severe. On the second day of cefdinir therapy, symptoms (wheeze) progressed to status asthmaticus which was treated with a respirator. Shock was suggested by the development of dyspnea and cyanosis. Blood gases were normal. The patient was on theophylline and procaterol, as well as a mucolytic and antitussive before cefdinir was begun. A composite report from our Worldwide Adverse Events Reporting System (WAERS) database is attached, along with lists of previous reports of asthma and shock. The events were classified as serious and unexpected, and the reporting physician in Japan considered both events possibly related to cefdinir. The Parke-Davis medical reviewer considered the events a progression of the underlying disease and not likely related to cefdinir. However, since the reporting physician considered the events possibly related, we are submitting the case as an IND safety report. Also, pursuant to 21 CRF 312.32 (c), all investigators participating in cefdinir studies will be notified of these events.
		D. Scott	
B06720	188	Tue, Feb 15, 1994 M. Lumpkin	Protocol Amendments: New Protocol/New Investigator New Protocol 983-056 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus Penicillin V in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients. New Center 983-056-004. Princ. Invest: [redacted] New Investigator: 983-005-031 Princ. Invest: [redacted]
		D. Scott	
B06720	189	Fri, Feb 25, 1994 M. Lumpkin	Protocol Amendments: New Investigator New Investigator: 983-004-075, 983-004-076, 983-004-077 New Investigator: 983-005-028 New Investigator: 983-056-001, 983-056-002, 983-056-005, 983-056-009, 983-056-011
		D. Scott	
B06720	190	Mon, Mar 07, 1994 M. Lumpkin	Protocol Amendment: New Investigator New Investigator: PR. 983-056-003, 983-056-006, 983-026-007 Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted]
		D. Scott	

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B06862	191	Mon, Mar 14, 1994 M. Lumpkin D. Scott	Information Amendments: Pharmacology/Toxicology/Clinical (7) Research Reports Submitted See Research Report List for RR#, author, date, title One correction submitted to RR-720-02983 IB
B06862	192	Thu, Mar 31, 1994 M. Lumpkin D. Scott	Protocol Amendments: New Investigator/Change in Protocol New Investigator: 983-005-032, 983-005-033, 983-005-034, 983-005-035 Orig. Filed 10/19/92 (Ser. No. 123) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-056-008, 983-056-010, 983-056-012, 983-056-013, 983-056-014 Orig. Filed 2/14/94 (Ser. No. 188) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest. [redacted] Princ. Invest: [redacted] 983-053-000 - AMENDMENT 1 Orig. Filed 10/11/93 (Ser. No. 172) [redacted] has assumed responsibility as principal investigator, replacing [redacted]. for Protocol 983-004-053. Orig. Fiiled 4/10/92 (Ser. No. 094) Change of address for [redacted].D. Protocol 983-006-010 (see file) Change of IRB address for Protocol 983-004-070, 983-004-071 (see file) Added B. Ward as subinvestigator for Protocol 983-004-015 Orig. Filed 11/27/91 (Ser. No. 070). [redacted] as subinvestigators for Protocol 983-006-010 Orig. Filed 5/22/92 (Serial No. 099). [redacted] subinvestigor for Protocol 983-004-071 Orig. Filed 1/19/94 (Serial No. 185).

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B06862	193	Fri, Apr 08, 1994 M. Lumpkin D. Scott	Request for Review of Trade Name We are requesting that the CDER Labeling and Nomenclature Committee review our proposed trade name for cefdinir, "Omnicef." Cefdinir is a broad-spectrum, semisynthetic cephalosporin for oral use. Application for the trademark Omnicef was made to the Patent and Trademark Office on August 14, 1992. Omnicef was published in the Trademark Digest on May 18, 1993, and the trademark was allowed on December 7, 1993. We would appreciate a review at the earliest possible committee meeting, which we understand will likely be in May.
B06862	194	Fri, Apr 08, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Protocol New Protocol 983-044 entitled, A Pharmacokinetic Study of Cefdinir in Patients on Chronic Haemodialysis. Princ: Invest: [redacted]CGP
B06862	195	Tue, Apr 12, 1994 M. Lumpkin D. Scott	General Correspondence: Meeting Minutes Attached are Parke-Davis' minutes of our CANDA meeting of March 9, 1994. We would appreciate any comments you have and a copy of Agency minutes if available. Desk copies are included for each FDA participant.
B06862	196	Mon, Apr 25, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Investigator New Invest: 983-005-036 Orig. filed: 10/19/92 (Serial No. 123) Principal Invest: [redacted]
B06862	197	Thu, Apr 28, 1994 M. Lumpkin D. Scott	IND Safety Report: Initial Written Report In accordance with 21 CFR 312.32 (c), we are submitting an initial IND Safety Report on cefdinir (Adverse Event No. 081-0983-940064-00). The event is ileus. It did not occur in an IND study, rather from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This unlabelled event involved or prolonged inpatient hospitalization and was considered definitely related to cefdinir, but not serious, by the reporting physician. The Parke-Davis Medical Reviewers consider the available information insufficient for assessment. However, as the report meets the FDA definition of serious, is unlabelled and was considered related to cefdinir by the reporting physician, it is being submitted as an IND safety report. There have been no prior similar reports to our Worldwide Adverse Events Reporting System (WAERS).

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B06862	198	Wed, May 25, 1994 M. Lumpkin D. Scott	IND Safety Report: Follow-up to a Written Report Please refer to our submission of an Initial Written IND Safety Report on April 28, 1994 (Serial No. 197), in which we reported a case of ileus from post-marketing experience in Japan (Adverse Event No. 081-0983-940064-00). Ileus was reported on Day 2 of treatment with cefdinir for a post-operative wound infection. Additional information we have now obtained indicates that the patient became constipated 10 days after surgery for an incisional hernia, with the ileus developing 14 days after the surgery. The reporting physician considered the ileus secondary to severe abnormal bowel movement due to cefdinir; drug attributability has been changed from "definitely related" to "probably related" by the physician. The Parke-Davis medical reviewers consider the ileus unlikely to be related to cefdinir. A revised reporting form is attached, with the new information highlighted. The original report is also included for reference. With the receipt of this additional information, investigators have been informed of the event pursuant to 21 CFR 312.32(c).
B06862	199	Tue, Jun 14, 1994 M. Lumpkin D. Scott	Information Amendment: Clinical We are writing to inform you of a probable case of rheumatic fever in a patient in the cefdinir 5-day pediatric pharyngitis study, 983-056. Although this event is not reportable under 21 CFR 312.32(c), we felt we should notify the investigators and you regarding this occurrence. The letter sent to the investigators is attached. We will continue to review this case, and any additional significant information will be forwarded to you and the investigators. Enrollment in Study 983-056 is about 90% complete, and the study will finish as planned.

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B06862	200	Wed, Jun 15, 1994 M. Lumpkin	IND Safety Report: Initial Written Report	Please refer to our IND 34,738, for Cefdinir Capsules and Suspension. In accordance with 21 CFR 312.32 (c), we are submitting an IND Safety Report on cefdinir. This follows a 3-day telephone report made to Mr. Carmen Debellas on June 7, 1994. The events are Steven-Johnson Syndrome, Drug-Induced Hepatic Dysfunction, and Acute Respiratory Failure. They did not occur in an IND study, rather from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This is a case of a 59-year-old woman who developed a Steven-Johnson type eruption, hepatic dysfunction and acute respiratory failure after 2 days treatment with 300 mg cefdinir for alveolar pyorrhea. She was also receiving diclofenac sodium which is labelled for similar adverse events. The referenced events were considered life threatening and definitely related to cefdinir by the reporting physician. Steven-Johnson Syndrome and Drug-Induced Hepatic Dysfunction are in Investigator's Brochure; Acute Respiratory Failure is unlabelled. A list of prior similar reports to our Worldwide Adverse Events Reporting System (WAERS) follows the reporting form.
		D. Scott		
B07038	201	Mon, Jun 20, 1994 M. Lumpkin	General Correspondence: Meeting Materials	We are submitting information in preparation for our next meeting with your Division on the cefdinir CANDA. This meeting is scheduled for June 30, 1994 at 9:00 a.m. (Room 12B-21). We have listed follow-up items from our previous meeting on March 9, 1994 that we would like to discuss. We have also included updated sample patient summaries (case report tabulations) with accompanying CRF's for three studies; uncomplicated UTI (Study 983-002), acute bronchitis (Study 983-038), and community-acquired pneumonia (Study 983-004). We understand that the following individuals will be attending from FDA: [redacted]er [redacted]roject Manager [redacted]M.D., former Medical Officer [redacted]M.S., Statistician If a new medical officer is assigned by the time of the meeting, it would be useful if he or she could also attend. [redacted] M.D. The following individuals will attend from Parke-Davis: [redacted]Sr. Systems Analyst, Research Information Systems [redacted], M.S., Sr. Clinical Scientist, Clinical Research Drusilla Scott, Ph.D., Director, Worldwide Regulatory Affairs [redacted] Sr. Director, Clinical Research [redacted]Associate Director, Biometrics
		D. Scott		

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B07038	202	Tue, Jul 12, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Protocol New Protocol 983-058 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 10-Day Regimen of Penicillin V in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Adult Patients. New Centers 983-058-010: Princ. Invest: [redacted]983-058-001: Princ. Invest: [redacted] 983-058-002: Princ. Invest: [redacted]. 983-058-003: Princ. Invest: Victor A. Elinoff, M.D. , 983-058-004: Princ. Invest: [redacted]M.D., 983-058-006: Princ. Invest: [redacted]., and PR. 983-058-009: Princ. [redacted]
B07083	203	Thu, Jul 14, 1994 M. Lumpkin D. Scott	Information Amendments: Chemistry/Microbiology/Pharmacology/Toxicology/Clinical (10) Research Reports submitted. See Research Report List for RR#, date, author, title Resumbitted 720-02983 with revised pages i, iii, v-viii, 9 and 21
B07090	204	Fri, Jul 15, 1994 M. Lumpkin D. Scott	IND Safety Reports: Initial Written Reports In accordance with 21 CFR 312.32 (c), we are submitting two IND Safety Reports on cefdinir. These follow a 3-day telephone report made to [redacted] of your Division on July 13, 1994. Report 1 The event reported (Adverse Event No. 081-0983-940018-01), was pseudomembranous colitis, and the patient died. This did not occur in an IND study, rather it was reported from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. A 70-year-old female with a history of a cerebral embolism, heart failure, asthma, and a gastric ulcer developed a reported pseudomembranous colitis 12 days after receiving 11 days of treatment with 300 mg cefdinir daily. She died 44 days post-treatment. Follow-up information indicated that the patient died of heart failure, pneumonia, and poor nutritional state secondary to frequent diarrhea. Though pseudomemebranous colitis was ruled out by negative tests for C. difficile and C. difficile toxin, the reporting physician did not change the event term. Report 2 The events reported (Adverse Event No. 081-0983-940020-01), were gastrointestinal (GI) hemorrhage, hepatic dysfunction, and eruption (disseminated erythema). These did not occur in an IND study, rather they were reported from post-marketing experience in Japan. Initially, the report was of an 84-year-old man with a history of cerebrovascular disease and hypertension who was hospitalized for an eruption and hepatic dysfunction during treatment with cefdinir for an upper respiratory tract infection. Follow-up information indicated that the patient had died of an upper GI hemorrhage (gastroscopic proven ulcer). Hematemesis and melena appeared 4 days after steroids were begun for the eruption (8 days after cefdinir was discontinued) and death occurred 15 days after cefdinir was discontinued. The completed reporting forms for each of the patients are attached.

CI#:	983
Generic:	
Product Name:	Cefdinir
Sub Date:	4/30/90
Appr Date:	

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B07090	205	Thu, Jul 21, 1994	Information Amendment: Chemistry, Manufacturing and Controls
		M. Lumpkin	Attached is an information amendment to our IND 34,738, for Cefdinir Capsules and Suspension, updating the manufacturing processes for Cefdinir Capsules and Powder for Oral Suspension. The manufacturing processes described in earlier amendments, dated April 18, 1991 and August 21, 1991 (Serial No. 033 and 054, respectively), for capsules (100, 200 and 300 mg) have been modified slightly in the Preparation of Polyoxyl 40 Stearate/Magnesium Stearate Mixture. In step a, the polyoxyl 40 stearate solution is allowed to cool below 40 C instead of 45 C. This solution is then slowly added to the magnesium stearate in the P-K blender instead of at a rate of 300 to 500 g/min in step b. In step e, the blending time is refined to 10 minutes rather than 5-10 minutes. The process for Preparation of Capsules remains unchanged except the amount of granulation for encapsulation for each strength is described. These changes are described in the attachment. (See letter for more info.)
		P. Chen	
B07090	206	Mon, Aug 08, 1994	Information Amendments: Pharmacology/Toxicology; Clinical
		L. Gavrilovich	Submitted (1) Research Report See Research Report list for RR#, date, author, title Correction to RR-X 720-02983 submitted (orig. submitted 2/18/92, Ser. No. 087)
		D. Scott	

Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B07090	207	Tue, Aug 09, 1994 L. Gavrilovich	Protocol Amendments: New Investigator/Change in Protocol

New Invest: 983-005 Prot. Orig. Filed 10/12/92 (Ser. No. 123)
PR. 983-005-037, Princ. Invest: [redacted]

New Invest: 983-058 Prot. Orig. Filed 7/12/94 (Ser. No. 202)
PR. 983-058-005, Princ. Invest: [redacted]
PR. 983-058-007, Princ. Invest: [redacted]
PR. 983-058-008, Princ. Invest: [redacted]

PR. 983-053-000 - AMENDMENT 2 Orig. Filed 10/11/93 (Ser. No. 172)

PR. 983-026-033 Added coinvestigators: [redacted]
Orig. Filed 11/5/93 (Ser. No. 174)

PR. 983-026-050 - ADDENDUM D Orig. Filed 12/9/93 (Ser. No. 181)

PR. 983-044-000 - AMENDMENT 1 Orig. Filed 4/8/94 (Ser. No. 194)

PR. 983-004-061 - [redacted] has assumed responsibilities as principal investigator for this study, replacing [redacted] Orig. Filed 3/19/93 (Ser. No. 147)

PR . 983-004-040 Added subinvestigator: [redacted]
Orig. Filed 12/19/91 (Ser. No. 074)

PR. 983-004-015 Added subinvestigator: [redacted]
Orig. Filed 1/11/92 (Ser. No. 102)

PR. 983-011-032 Added subinvestigator: [redacted]
Orig. Filed 1/11/92 (Ser. No. 102)

PR. 983-006-022 Added subinvestigators: [redacted]
Orig. Filed 8/7/92 (Ser. No. 111)

PR. 983-004-064 Added subinvestigators: [redacted]
Orig. Filed 12/22/92 (Ser. No. 135)

PR. 983-004-063 Added subinvestigators: [redacted]
Orig. Filed 2/19/93 (Ser. No. 142)

PR. 983-051-008 Added subinvestigator: [redacted]
Orig. Filed 5/19/93 (Ser. No. 152)

PR. 983-053-000 Added subinvestigator: [redacted]
Orig. Filed 10/11/93 (Ser. No. 172)

PR. 983-004-072 Added subinvestigators: [redacted]

IND/NDA/DMF#:	34,738 IND	Doc Type:	FDA CORRESPONDENCE
		SubType:	IND
CI#:	983	Sub Date:	4/30/90
Generic:		Appr Date:	
Product Name:	Cefdinir		

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
			Orig. Filed: 1/19/94 (Ser. No. 185) PR. 983-056-005 Added subinvestigators: [redacted] Orig. Filed 2/25/94 (Ser. No. 189) PR. 983-056-006 Added subinvestigators: [redacted]y, [redacted] Orig. Filed 3/7/94 (Ser. No. 190) PR. 983-056-014 Added subinvestigator: [redacted] Orig. Filed 3/31/94 (Ser. No. 192) PR. 983-005-034 Added subinvestigators: [redacted]. [redacted] Orig. Filed 3/31/94 (Ser. No. 192) PR. 983-056-012 Added subinvestigator: [redacted] Orig. Filed 3/31/94 (Ser. No. 192)
		D. Scott	
B07090	208	Tue, Aug 16, 1994	Annual Report
		L. Gavrilovich	Attached for your information and files is the Annual Report for IND 34,738, Cefdinir (CI-983) Capsules and Suspension. This report covers the period June 7, 1993 through June 6, 1994.
		D. Scott	
B07214	209	Mon, Aug 22, 1994	Information Amendment: Clinical
		L. Gavrilovich	(1) Research Report Submitted See Research Report List for RR #, date author, title
		D. Scott	

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B07222	210	Thu, Sep 15, 1994 L. Gavrilovich	General Correspondence: Briefing Package for Meeting We are submitting a briefing package for our meeting to review the clinical plan for cefdinir. The meeting is scheduled for September 22, 1994 at 10:00 a.m. We understand the following persons will attend from FDA: [redacted] - Supervisory Medical Officer, DAIDP [redacted] - Project Manager, DAIDP [redacted]D. - Supervision Statistician, Division of Biometrics [redacted] - Medical Officer, DAIDP [redacted] - Statistician, Division of Biometrics The following will attend from Parke-Davis: [redacted] - Sr. Clinical Scientist, Clinical Research Drusilla Scott, Ph.D. - Director, FDA Liaison, Worldwide Regulatory Affairs [redacted] Sr. Director, Clinical Research [redacted] - Director, Biometrics Desk copies of the packages are enclosed for each FDA attendee. E. Scott
B07222	211	Thu, Sep 29, 1994 L. Gavrilovich, M.D. D. Scott, Ph.D.	General Correspondence: Meeting Minutes Minutes of meeting held with Division on September 22, 1994. We would appreciate any comments you have on the minutes, plus a copy of the Agency minutes when available. Please note that the meeting generated action items for both the Agency and Parke- Davis.
B07222	212	Fri, Sep 30, 1994 L. Gavrilovich, M.D. D. Scott	Protocol Amendment: New Investigator Pr. 983-058-011: Prin. [redacted] Pr. 983-058-012: Prin. Inv.: [redacted] Orig. filed July 12, 1994 (Serial No. 202)
B07222	213	Thu, Oct 13, 1994 M. Lumpkin, M.D. D. Scott	Protocol Amendment: New Investigator Pr. 1003-058-013: Prin. Inv.: [redacted] Orig. filed: July 12, 1994 (Serial No. 202)

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B07222	214	Fri, Oct 21, 1994 L. Gavrilovich P. Chen	Information Amendment: Chemistry, Manufacturing and Control We were informed [redacted] 34,738, for Cefdinir Capsules [redacted] The cover letter of the amendment is attached. We, hereby, respectively request the Agency to reference this update in support of our IND. Should you have any questions regarding this submission, please contact me at 313/996-2623 or FAX 313/996-7890.
B07222	215	Thu, Nov 10, 1994 L. Gavrilovich D. Scott	General Correspondence: Review of Trade Name We are requesting that the CDER Labeling and Nomenclature Committee reconsider the issues discussed in its May 9, 1994 review of the proposed trade name "Omnicef" for cefdinir, and recommend approval of the name to the Division. The attached narrative provides background and responds to the concerns raised by the Committee, with a focus on the major concern - [redacted]
B07222	216	Wed, Dec 07, 1994 L. Gavrilovich D. Scott	Protocol Amendment: New Protocol; Information Amendment: Chemistry/Microbiology We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-050-000, entitled "A Study of the Mass Balance and Metabolism of [14C]CI-983 (Cefdinir) in Healthy Male Volunteers." Also included is Amendment 1 to the protocol which replaces the second paragraph in Section VI. A., Dosing Schedule. Drug will now be pre-weighed by Parke-Davis rather than prepared at the study site.
B07222	217	Mon, Dec 19, 1994 L. Gavrilovich D. Scott	Protocol Amendments: New Investigators Pr: 983-058-014: Prin. Inv.: [redacted] Pr.: 983-058-015: Prin. Inv.: [redacted] Pr.: 983-058-016: Prin. Inv. [redacted] Pr.: 983-058-017: Prin. Inv. [redacted] Pr: 983-058-018: Prin. Inv. [redacted] Pr. 983-058-019: Prin. Inv. [redacted] Pr. 983-058-020: Prin. Inv. [redacted] Pr. 983-058-021: Prin. Inv. [redacted] Pr. 983-058-022: Prin. Inv. [redacted] Pr. 983-058-023: Prin. Inv. [redacted] Original submitted 7/12/94 (Ser. No. 202)

SubType: IND

Cl#: 983 Sub Date: 4/30/90

Generic: Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B07222	218	Wed, Dec 21, 1994 M. Lumpkin	Protocol Amendments: New Investigator/Change in Protocol [redacted] has assumed responsibilities as principal investigator for Study 983-004-026 replacing [redacted] Center filed on 12/12/91 (Ser. No. 073). Additional Subinvestigators: Pr. 983-004-012: New Subinvestigators: [redacted] Study Center submitted on 12/19/91 (Ser. No. 074) Pr.: 983-004-026: New Subinvestigators: [redacted] Study Center submitted on 12/12/91 (Ser. No. 073) Pr. 983-004-027: New Subinvestigators: [redacted] Study Center submitted on 4/10/92 (Ser. No. 094) Pr. 983-004-040: New Subinvestigator: [redacted] Study Center submitted on 12/19/91 (Ser. No. 074) Pr. 983-004-053: New Subinvestigators: [redacted] Study Center submitted on 3/31/94 (Ser. No. 192) Pr. 983-004-064: New Subinvestigators: [redacted] Study Center submitted on 12/22/92 (Ser. No. 135) Pr. 983-004-070: New Subinvestigators: [redacted] Study Center submitted on 1/19/94 (Ser. No. 185) Pr. 983-004-040 address change for [redacted]
		D. Scott	
B07222	219	Mon, Jan 16, 1995 L. Gavrilovich	General Correspondence Enclosed is a background package for a meeting to be held on January 24, 1995 at 10:00 A.M. in Room 12B-45 (Parke-Davis will set up the CANDA in this room at 9:30). During the meeting, Parke-Davis will demonstrate the projected capabilities of the Cefdinir CANDA. The background package briefly describes the attributes to be demonstrated.
		D. Scott	
B07222	220	Wed, Feb 08, 1995 L. Gavrilovich	Information Amendment: CMC Attached Research Report 956-00188 describes a proposed market-image for the 300 mg capsules. See file for description of new capsule and manufacturing and site. Attached RR 730-02289 rpovides an alternate UV method in conjunction with an IR procedure for the identificaiton of drug substance.
		P. Chen	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B07222	221	Mon, Feb 13, 1995 L. Gavrilovich D. Scott	General Correspondence Attached are the minutes of a meeting we held with the Division on the cefdinir CANDA on January 24, 1995. We appreciate the opportunity to have had this meeting. We would appreciate any comments you have on the minutes, plus a copy of any Agency minutes when available. Dr. Soreth indicated that she would provide some working definitions on significant laboratory changes form baseline; we would appreciate receiving these at her earliest convenience to plan a further discussion on safety.
B07472	222	Tue, Feb 21, 1995 L. Gavrilovich D. Scott	Information Amendments: Clinical/Chemistry/Microbiology/Pharmacology/Toxicology (14) Research Reports submitted See Research Report list for RR#, date, author, title
B07601	223	Tue, Mar 28, 1995 L. Gavrilovich D. Scott	Information Amendments: Chemistry/Microbiology/Clinical/Pharmacology/Toxicology (7) Research Reports submitted See Research Report log for authors, dates, titles and RR#
B07663	224	Mon, Apr 24, 1995 L. Gavrilovich D. Scott	Information amendments: Chemistry/Microbiology, Pharmacology/Toxicology, Clinical Attached for your information and files are nine research reports entitled:
B07665	225	Mon, May 01, 1995 C. Debellas S. Brennan	General Correspondence: Request for Pre-NDA Meeting Reference is made to IND 34,738 for Cefdinir Capsules and Suspension and to your telephone conversation of March 29, 1995 with Paul Chen of Parke-Davis requesting a pre-NDA meeting to discuss the Chemistry, Manufacturing and Controls sections of the NDAs for the respective dosage forms. We request a meeting (1.5 to to 2 hours) with [redacted] (Supervisory Chemist), [redacted] (Reviewing Chemist) and you be arranged.

SubType: IND

CI#: 983 Sub Date: 4/30/90

Generic: Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B07665	226	Tue, May 16, 1995 L. Gavrilovich	Pre-Meeting Materials Reference is made to the previous correspondences between [redacted] Division and [redacted] and myself of Parke-Davis regarding a pre-NDA meeting to discuss the Chemistry, Manufacturing and Controls section of the NDAs on May 1 and 11, 1995. This letter is to confirm our pre-NDA meeting with [redacted]s on May 31, 1995 at 10:30 A.M. (Room 12B21, Parklawn). Attached are the pre-meeting materials requested. We also request an overhead slide projector in the meeting room. The proposed Parke-Davis attendees are: [redacted], Ph.D. Senior Director, Regulatory Affairs [redacted] Ph.D. Senior Manager, Regulatory Affairs [redacted], Ph.D. Director, Product Development [redacted] Ph.D. Director, Product Development [redacted] Ph.D. Senior Research Associate, Chemical Development [redacted] Ph.D. Director, Product Development
		S. Brennan	
B07665	227	Mon, May 22, 1995 L. Gavrilovich	Pre-Meeting Materials Update Reference is made to the Pre-NDA meeting Materials for Cefdinir Capsules and Suspension submitted on May 16, 1995. Due to electronic transmission errors, three figures in Section 3: Drug Product B and C were inadvertently omitted. Enclosed, please find the replacement Section 3: Drug Product B and C portion of the Pre-NDA meeting Materials.
		S. Brennan	
B07665	228	Fri, May 26, 1995 L. Gavrilovich	Information Amendment This is an information amendment to our IND 34,738, for Cefdinir Capsules and Suspension, which updates the manufacturing and controls information for capsules. Based on experiences with the equipment of our contract manufacturer, [redacted] we are revising the drying temperature range in step c. for the preparation of Polyoxyl 40 Stearate/Magnesium Stearate Mixture, but the final specification remains the same (LOD of not more than 2.5%). The change is described below: c. Dry the wet mass from step b. in a drying oven between 24 and 45 C to an LOD of not more than 2.5%. In addition, we are deleting the Loss on Drying test in the Specifications and Test Method Section for the finished product because the final granulation is manufactured by a dry blending and compaction process.
		P. Chen	

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
	229	Tue, Jun 13, 1995 L. Gavrilovich D. Scott	Request for pre-NDA Meeting Request of a pre-NDA meeting to discuss content & format of our upcoming NDA's for Cefdinir Capsules and Oral Suspension. These NDA's will be submitted 2Q1996. This meeting will not cover NDA Items 3 and 4.
B10108	330	Tue, Jun 20, 1995 L. Gavrilovich D. Scott	RR 720-03489, 720-00124, 730-02289; 939-00669 Cefdinir Drug Substance: IND Information Amendment for Identification By UV", by S Priebe, dated February 22, 1995 (Research Report No. 730-02289) Validation of Uniformity of Dosage Units by Weight Variation Test Method for CI-983 (Cefdinir) 300 mg Capsules", by [redacted] Research Report No. 939-00669) A Study to Evaluate the Potential Pharmacokinetic Interactions Between Maalox® and Cefdinir (CI-983) (Protocol 983-030-0)", by [redacted] 15, 1995 (Research Report 744-00124) Listings for a Phase 3, 10-Day, Investigator-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Cephalexin in the Treatment of Pediatric Patients with Uncomplicated Skin and Skin Structure Infections (Protocol 983-13)", [redacted], dated March 15, 1995 (Research Report 720-03489) A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Patients with Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-7)", by [redacted] Research Report 720-03459)
B10195	0	Fri, Jun 30, 1995 M. Thomas D. Scott	Follow-up to Request Enclosed are the case report forms you requested. The forms are followed by the laboratory findings, and when applicable, a site-generated change form.
B10195	231	Fri, Jul 14, 1995 M. Fanning D. Scott	Protocol Amendment: New Protocol We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-068 entitled "A Pharmacokinetic Study of Cefdinir in Patients on Chronic Hemodialysis". We are initiating this study with Center 000.
B10195	232	Mon, Jul 17, 1995 M. Fanning D. Scott	Response to FDA Request for Information Please refer to IND 34,738 for cefdinir capsules and suspension and to your May 28, 1991, correspondence that commented on our clinical protocols for the treatment of uncomplicated urinary tract infections and lower respiratory tract infections, which were submitted to FDA on September 24, 1990. We discussed the issues with Linda Sherman, MD, Medical Reviewer, shortly after the IND submission. When we received these comments a year later, most issues were moot. Nevertheless, we are formally responding at this time to complete and close the file on this correspondence before the NDA is submitted.

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B10195	233	Mon, Jul 17, 1995 M. Fanning D. Scott	Response to FDA Request for Information Please refer to IND 34,738 for cefdinir capsules and suspension, and to your May 28, 1991 correspondence that provided comments on our original IND submission of May 2, 1990.
B10209	234	Tue, Jul 18, 1995 M. Fanning D. Scott	Information Amendments: Clinical "Listings For A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Patients With Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-7)", by L. Bond, C. Keyserling, et al., dated June 9, 1995 (Research Report 720-03460)
B10214	235	Thu, Jul 27, 1995 M. Fanning D. Scott	RR-720-03467 and RR-720-03468 An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Pediatric Patients with Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-51), by [redacted] dated June 19, 1995 (Research Report No. 720-03467) Patient Listings for an Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) versus Penicillin V-K in the Treatment of Pediatric Patients with Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-51), by [redacted] dated June 27, 1995 (Research Report No. 720-03468)
B10251	236	Thu, Aug 03, 1995 M. Fanning D. Scott	re: Pre-NDA meeting Attached is our background package for the pre-NDA cefdinir meeting on August 11, at 1:00 p.m., in Conference Room A of the Parklawn building. This meeting is being held to discuss the structure, format, and presentation of data for the 1996 cefdinir capsule and cefdinir suspension NDA's.
B10251	237	Wed, Aug 09, 1995 M. Fanning D. Scott	New Investigators Regarding Protocol 983-004: Change of address for [redacted], Center 983-004-014. Numerous new subinvestigators added. Regarding Protocol 983-005: Added [redacted] as coinvestigator to 983-005-010, and [redacted] as coinvestigator to 983-005-030. Regarding Protocol 983-051: Addendum A Regarding Protocol 983-006: Addresses of [redacted] 983-006-041 and of Dr. [redacted] 983-006-020, have changed. New subinvestigators added to 010 and 018. Regarding 983-007, 983-008, 983-101, 983-100, 983-013, 983-019, 983-026, 983-037, 983-038, 983-048, 983-051, 983-056, and 983-058, new subinvestigators were added.
B10251	238	Thu, Aug 24, 1995 M. Fanning D. Scott	Protocol Amendments Nine Research Reports: 720-03510, 720-03564, 764-02364, 764-02365, 764-02366, 764-02367, 764-02368, 764-02369 and 764-02404

IND/NDA/DMF#:	34,738 IND	Doc Type:	FDA CORRESPONDENCE
		SubType:	IND
CI#:	983	Sub Date:	4/30/90
Generic:		Appr Date:	
Product Name:	Cefdinir		

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B10251	239	Tue, Aug 29, 1995	Information Amendment: CMC
		M. Fanning	This amendment describes the manufacturing and controls information for the market-image 125 and 250 mg/5 ml strawberry-flavored powder for oral suspension formulations. These market-image suspensions will be manufactured and tested physically and chemically by our contract manufacturer, [redacted] Alternatively, physical and chemical testing may be performed at our Rochester, MI facility. The microbiological testing will be performed by a contract laboratory, [redacted] Each batch of the oral suspension will be labeled and dispensed from Clinical Pharmaceutical Operations at Ann Arbor, MI. Alternatively, the labeling may be conducted at our [redacted] This information is described in Section 1.1 of the attached report.
		P. Chen	
B10473	240	Thu, Sep 14, 1995	Annual Report
		M. Fanning	Annual Report
		D. Scott	
B10473	241	Fri, Sep 29, 1995	Protocol Amendments: New Protocol
		M. Fanning	We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-066 entitled, A Single-Dose Bioequivalence Study Comparing 300-mg Cefdinir Capsules Used in Clinical Studies to Market-Image 300-mg Cefdinir Capsules. We are initiating this study at Parke-Davis's Community Research Clinic.
		D. Scott	
B10473	243	Wed, Oct 11, 1995	IND Safety Report: Initial Written Report
		M. Fanning	we are submitting an initial 10-Day IND Safety Report. The adverse event being reported is cholestasia. It was reported from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. Cholestasia was reported in a 3-year-old girl with a history of infantile CMV hepatitis who received cefdinir for 7 days for treatment of fever, coughing, and diarrhea. Liver biopsy findings were compatible with drug-induced cholestasis. [redacted]
		D. Scott	
B10473	242	Wed, Oct 11, 1995	Protocol Amendment: New Protocol
		M. Fanning	New Protocol 983-059 entitled, A Double-Blind, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 7-Day Regimen of Loracarbef in the Treatment of Acute Exacerbations of Chronic Bronchitis in Adult Patients. New Centers 983-059-003, 983-059-004, 983-059-008, and 983-059-017.
		D. Scott	
B10473	244	Tue, Oct 17, 1995	Information Amendment: Clinical
		M. Fanning	Seven Research Reports: 720-03465, 720-03466, 720-03570, 720-03571, 720-03572, 750-00268, and 764-02446 and Investigator Brochure Update, dated 6/26/95
		D. Scott	
B10473	245	Wed, Oct 25, 1995	General Correspondence: Meeting Minutes
		M. Fanning	Attached are the minutes of the cefdinir pre-NDA meeting on issues other than CMC.
		D. Scott	

Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B10844	247	Mon, Nov 13, 1995 M. Fanning P. Chen	Information Amendment: CMC Based on our manufacturing experience with both the 125 and 250 mg/5ml strengths of Cefdinir for Oral Suspension, we propose the following revisions to the specifications for these products
B10844	246	Mon, Nov 13, 1995 M. Fanning D. Scott	Protocol Amendments: New Protocol, New Investigators New Protocol 983-067 entitled, A Single-Dose Bioequivalence Study of Cefdinir Comparing 125 mg/5 ml Market-Image Suspension to the 125 mg/5 ml Suspension Used in Clinical Trials. Regarding Protocol 983-059: New Centers 983-059-001, 983-059-002, 983-059-007, 983-059-009, 983-059-010, 983-059-015, 983-059-019, 983-059-021, 983-059-023, 983-059-025.
B11391	248	Tue, Dec 05, 1995 M. Fanning D. Scott	Information Amendments: Clinical Three Research Reports: 744-00206, 720-03453 and 720-03454
B12264	249	Thu, Dec 07, 1995 M. Fanning P. Chen	Information Amendment: CMC Reference is made to our IND 34,738 for Cefdinir Capsules & Suspension & to the pre-NDA meeting on CMC issues with Drs. S. Roy, supervisory chemist, V. Shetty, reviewing chemist, and Mr. C. Debellas, CSO of your Division on 5/31/95. Attached, please find two [redacted]eports entitled, Single Dose Toxicity Study of A Related Compound of Cefdinir In Mice (Intravenous Dosing), GLR920020 and Single Intravenous Dose Toxicity Study of Related Compounds of FR80482, GLR950408 for related compounds XII, XIII & XV.
B12264	250	Mon, Dec 11, 1995 M. Fanning D. Scott	Protocol Amendments: New Protocol, New Investigators New Protocol 983-060 entitled, A Double-Blind, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 10-Day Regimen of Cefprozil in the Treatment of Acute Exacerbations of Chronic Bronchitis in Adult Patients. New Center 983-060-002. New Protocol 983-068 entitled, A Pharmacokinetic Study of Cefdinir in Patients on Chronic Hemodialysis. New Center 981-068-002. Regarding Protocol 983-059: New Centers 983-059-005, 983-059-006, 983-059-011, 983-059-012, 983-059-014, 983-059-016, 983-059-020, 983-059-021, 983-059-022 and 983-059-024.
B12264	251	Tue, Dec 12, 1995 M. Fanning D. Scott	Protocol Amendments: New Protocol New Protocol 983-065 entitled, An Open-Label Multicenter Study of a 5-Day Regimen of Cefdinir in the Treatment of Acute Suppurative Otitis Media in Pediatric Patients. New Centers 983-065-001 and 983-065-010.

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B12274	252	Fri, Jan 12, 1996 M. Fanning D. Scott	Information Amendment: Clinical, Chemistry\Microbiology Four Research Reports: 744-00145, 744-00213, 744-00214 and 720-03632
B12568	253	Mon, Jan 15, 1996 M. Fanning D. Scott	Protocol Amendment: New Investigator Regarding Protocol 983-059: New Center 983-059-013 Regarding Protocol 983-060: New Centers 983-060-003, 983-060-004, 983-060-005, 983-060-006, 983-060-007, 983-060-008, 983-060-010, 983-060-012, 983-060-014, 983-060-015, 983-060-016, 983-060-017, 983-060-018, 983-060-019, 983-060-020 and 983-060-024 Regarding Protocol 983-065: New center 983-065-003
B12568	254	Fri, Feb 02, 1996 M. Fanning D. Scott	Information Amendments: Clinical, Pharmacology/Toxicology Six Research Reports: 744-00221, 764-02507, 764-02498, 764-02499, 764-02500, 764-02501
B12568	255	Thu, Feb 08, 1996 M. Fanning D. Scott	Protocol Amendment: New Investigators Regarding Protocol 983-060: New Centers 983-060-021 and 983-060-023 Regarding Protocol 983-065: New Centers 983-065-004, 983-065-007 and 983-065-009
B12568	256	Thu, Feb 08, 1996 M. Fanning D. Scott	IND Safety Report: Initial Written Report This written report follows a telephone report I made to Mr. Carmen Debellas of your Division on 2/7/96. The adverse events being reported are acute enterocolitis and myocardial infarction. They were reported from Japanese post-marketing experience rather than clinical trials with cefdinir. The fatal myocardial infarction was considered secondary to the massive fluid shifts caused by hypoproteinemia resulting from severe colitis. The 78-year old male had received cefdinir 300 mg/day for 15 days, and died on Day 18. The reporting physician considered these events possibly related to cefdinir and to minocycline and panipenem/betamipron which the patient had received before cefdinir.
B13132	257	Wed, Feb 21, 1996 M. Fanning P. Chen	Information Amendment: Chemistry/Microbiology This amendment provides additional toxicity information on related compounds II, III, IV, V, VII, VIII and Metabolite M-V as suggested [redacted] supervisory chemist, in the pre-NDA meeting of May 31, 1995, between representatives of Parke-Davis and your Division. Attached is Fujisawa report entitled, Acute Toxicity Study of Deterioration Product, Related Compounds and Metabolite of FR 80482 in Mice (Intravenous Dosing).

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B13132	258	Wed, Feb 21, 1996 M. Fanning D. Scott	Adverse Event No. 081-0983-960007. This reports describes a 66-year-old woman who was hospitalized for vomiting and hyoptension after a single 100 mg dose of cefdinir for the treatment of acute bronchitis. Approximately 6 and one-half hours later, the blood pressure of this woman had dropped to 90/68. The patient was treated with I.B. hydrocortisone and dopamine and recovered. Though hypotension is the dominant reaction of anaphylatic shock, the term hypotension is unlabeled under the policy of reporting what has been reported and not what we think has been reported.	IND Safety Report: Initial Written Report
B13132	259	Tue, Feb 27, 1996 M. Fanning P. Chen	As the development of these products progresses, an improved analytical method for the impurities/degradation products for capsule and suspension products has been developed and validated. This amendment updates the method described previously in the IND for impurities/degradation products.	Information Amendment: CMC
B13132	0	Thu, Feb 29, 1996 W. Foley D. Scott	Reference is made to you 2/7/96 correspondence to [redacted] of Warner-Lambert Company. Per your request, enclosed are copies of all documents relevant to research conducted by [redacted] for Protocol 983-004 on behalf of PD.	Response to FDA Request for Information
B13293	260	Wed, Mar 06, 1996 M. Fanning D. Scott	Research Report Nos. 720-03565, 720-03573, 720-03574, 720-03575, 720-03576, 720-03563, 720-03569, 720-03577, 744-00181 and 744-00212.	Information Amendments: Chemistry/Microbiology and Clinical
B13771	261	Mon, Mar 11, 1996 M. Fanning D. Scott	Attached are seven research reports: 720-03562, 720-03566, 720-03567, 720-03568, 720-03578, 720-03579, and 720-03348	Information Amendments: Chemistry/Microbiology and Clinical
B13828	262	Mon, Mar 18, 1996 M. Fanning D. Scott	Research Report No. 720-03456 entitled, A Phase 3, 10-Day, Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Cefaclor in the Treatment of Adult Patients with Community-Acquired Pneumonia (Protocol 983-4)	Information Amendments: Clinical
B14034	263	Fri, Mar 22, 1996 M. Fanning D. Scott	We propose to electronically submit CRFs for all patients in Phase 2/3 studies. We are also proposing to submit investigator curricula vitae electronically only. We are uncertain as to whether this requires a Center waiver or simply Divisional agreement, as the NDA regulations do not require the submission of curricula vitae in the NDA. Rather, the 1988 guidelines, "Guidelines for the Format and Content of the Clinical and Statistical Sections of a Application" request their submission.	General Correspondence: Request for Waiver

Cl#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B14034	264	Tue, Mar 26, 1996 M. Fanning D. Scott	Information Amendment: Clinical Correction to the Investigator's Brochure, Research Report No. 720-03510
B14034	265	Tue, Apr 02, 1996 M. Fanning D. Scott	IND Safety Report: Initial Written Report Adverse Event No. 081-0983-960012. The adverse events being reported are malaise and vomiting. They were reported from Japanese post-marketing experience rather than clinical trials with cefdinir. A 68-year old woman who received 100 mg cefdinir for lymphangitis experienced [redacted] hospitalized. The reporting physician considered the vomiting and malaise probably related to cefdinir. The Parke-Davis medical reviewer considered the events related to cefdinir. Although vomiting is listed in the Investigator's Brochure, t[redacted]
B14034	266	Tue, Apr 23, 1996 M. Fanning D. Scott	IND Safety Report: Initial Written Report Adverse Event No. 081-0983-960015. The adverse events being reported are hepatic encephalopathy and hepatic function disorder. While hepatic function disorder has been reported previously, hepatic encephalopathy has not. These events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. A 73-year old man received cefdinir 300 mg/day for 7 days for the treatment of cervical infections atheroma. Cefdinir was discontinued at this time, when enzyme elevations were noted. Forty-nine days post-treatment, he was hospitalized for hepatic encephalopathy and hepatic function disorder. The patient has not yet recovered. The reporting physician considered these events possibly related to cefdinir, but pravastatin sodium, benidipine hydrochloride, and benzbromarone were also considered suspect drugs. The Parke-Davis Medical reviewer considered the events possibly related to cefdinir.
B14034	267	Fri, Apr 26, 1996 M. Fanning P. Chen	Information Amendment: Chemistry, Manufacturing and Controls Attached is an information amendment (RR-REG 956-00217) to our IND 34,738, which updates the Chemistry, Manufacturing and Controls for cefdinir powder for oral suspension. During manufacture of the strawberry flavored suspension (Formulation 30) in accordance with the process described in the amendment of August 29, 1995 (Serial No. 239), we experienced segregation in the filling process.
B14738	268	Tue, Apr 30, 1996 M. Fanning D. Scott	Information Amendments: Clinical Two Research Reports: 720-03390 and 744-00255.
B14740	269	Thu, May 02, 1996 M. Fanning D. Scott	Information Amendment: Clinical Research Report No. 720-03463 entitled, A Phase 3, 10-Day, Investigator-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Amoxicillin/Clavulanate in the Treatment of Community-Acquired Bacterial Pneumonia (Protocol 983-26)

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B14881	270	Mon, May 06, 1996 M. Fanning D. Scott	Protocol Amendment: New Investigators New Centers 983-060-009, 981-060-011, 981-060-022, 981-060-025, 981-060-026, 981-060-027, 981-060-028, 981-060-029, 981-060-030, 981-060-031, 981-060-033 and 981-060-034. New Centers 983-065-002 and 983-065-006
B16310	271	Mon, May 06, 1996 M. Fanning D. Scott	Information Amendment: Clinical RR 720-03416
B16316	272	Thu, May 09, 1996 M. Fanning D. Scott	Information Amendment: Clinical RR 720-003378
B16682	273	Mon, May 13, 1996 M. Fanning D. Scott	Information Amendment: Clinical Research Report No. 720-03471.
B16682	274	Tue, May 21, 1996 M. Fanning D. Scott	General Correspondence: Request for Waiver - Follow-Up In our submission of 3/22/96, we requested a waiver of 21 CFR 314.50(f) for upcoming NDAs for Cefdinir Capsules and Cefdinir Suspension. This NDA requirement is for paper copies of case report forms (CFRs) for patients who died during a clinical study or who did not complete the study because of an adverse event. As a follow-up to this request, and according to FDA MAPP 6010.1, we also state that the electronic case report forms have been prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11, 59 FR 45160 (8/31/94). Paper copies of the CRF's will be maintained as required under 21 CFR 312.57(b).
B17956	275	Wed, Jun 05, 1996 M. Fanning D. Scott	Information Amendment: Clinical Research Report Nos. 720-03469, 720-03717, 744-00267 and a revised Investigator's Brochure, No. 720-03510.
B19958	276	Mon, Jul 08, 1996 M. Fanning D. Scott	Protocol Amendment: Change in Protocol, New Investigators Regarding Protocol 983-067: Amendment 1 Regarding Protocol 983-026: New Center 983-026-008 Regarding Protocol 983-059: New Center 983-059-018 Regarding Protocol 983-060: New Center 983-060-032
B20334	277	Tue, Jul 09, 1996 M. Fanning D. Scott	Information Amendment: Pharmacology\Toxicology, Clinical Research Report X 764-02474, 720-03461, 744-00259 and 720-03453.

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B20335		Wed, Jul 10, 1996 D. Scott J. Woodcock	Waiver of the requirements Waiver of the requirements for the submission of paper case report forms and/or case report tabulations. Waiver request granted.
B20804	278	Wed, Jul 24, 1996 M. Fanning D. Scott	Information Amendment: Clinical Updated Research Report No. 720-03364 entitled, A Phase 3, 10-Day, Double-Blind, Randomized, Comparative, Multicenter Study of Cedfinir (CI-983) Versus Cephalexin in the Treatment of Patients with Skin and Skin Structure Infections (Protocol 983-8).
B21248	279	Mon, Aug 19, 1996 D. Feigal, M.D. D. Scott	IND Safety Report: Initial Written Report Adverse Event No. 081-0983-960025, an initial 10-Day safety report on cefdinir for anaphylactoid reaction (fatal). This follows a telephone call to Mr. Carmen Dellas of your Division on 8/15/96. Although ß-lactam antibiotics are prominently labeled with warnings about anaphylaxis, which always has the potential to be life-threatening or fatal, it is the policy of Parke-Davis to consider the initial death it learns of as immediately reportable. This event was not reported from PD clinical studies, rather from post-marketing experience in Japan. As reported in the attached MedWatch form, a 69-year-old man with an upper respiratory tract infection received a single 300 mg dose of cefdinir and died several hours later. He was receiving several concomitant drugs. The reporting physician considered the anaphylactoid reaction possibly related to cefdinir. The PD medical reviewer considered the event unrelated to cefdinir. Other anaphylactoid reactions previously reported to PDs' WAERS are attached. Also, all participating investigators will be notified of this event.
B21248	280	Wed, Aug 21, 1996 D. Feigal P. Chen	Information Amendment: Chemistry, Manufacturing and Controls Amendment to Research Report Reg 730-02666.
B21248	281	Tue, Sep 17, 1996 D. Feigal D. Scott	Annual Report Annual Report
B21248	282	Fri, Sep 20, 1996 D. Feigal D. Scott	Protocol Amendment: New Protocol New Protocol 983-064 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 10-Day Regimen of Cefprozil in the Treatment of Acute Suppurative Otitis Media in Pediatric Patients. New Center 983-064-001: [redacted]
B21248	283	Fri, Oct 18, 1996 D. Feigal D. Scott	Protocol Amendments: New Investigators Regarding Protocol 983-060: New Centers 983-060-036 and 983-060-037. Regarding Protocol 983-064: New Centers 983-064-002, 983-064-003, 983-064-006, 983-064-007, 983-064-009, 983-064-010, 983-064-011, 983-064-013, 983-064-014, and 983-064-015.

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B21248	284	Wed, Nov 20, 1996	IND Safety Report: Initial Written Report
		D. Feigal	We are submitting an initial 10-Day safety report on cefdinir, AE 081-0983-960039. The adverse events being reported is erythema nodosum (combined with fever, fatigue, and function disorder). These events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form, a 38-year old woman who had received 7 days of cefdinir, 300 mg/day, for suppurative mastitis was hospitalized 3 days after discontinuing treatment for generalized fatigability, hepatic function disorder, fever, and erythema nodosum. She recovered from all events by Day 20.
		D. Scott	
B21248	285	Fri, Dec 06, 1996	Information Amendment: Clinical
		D. Feigal	Updated Investigator's Brochure, RR 720-03510.
		D. Scott	
B22694	286	Wed, Dec 11, 1996	Protocol Amendment: New Investigators
		D. Feigal	Regarding Protocol 983-059: New Center 983-059-024. Regarding Protocol 983-060: New Centers 983-060-006 and 983-060-035. Regarding Protocol 983-064: New Centers 983-064-005 and 983-064-008.
		D. Scott	
B22694	287	Tue, Dec 31, 1996	IND Safety Report: Initial Written Report
		D. Feigal	we are submitting an initial 10-day safety report on cefdinir (AE 081-0983-960048) for stomatitis (combined with fever and erythema). The events were not reported from PD clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form, a 48-year old woman who had received cefdinir for bronchitis developed stomatitis, erythema, and fever. She recovered, but died from breast cancer and metastatic liver cancer 11 days later. The reporting physician considered the stomatitis and erythema possibly related to cefdinir. Erythema is in the Investigator's Brochure for cefdinir; there have been no prior reports of stomatitis although there have been reports of skin disorders affecting the oral mucosa (Stevens-Johnson syndrome). The reporter did not consider the stomatitis a form of Stevens-Johnson syndrome.
		D. Scott	
B22694	288	Tue, Jan 07, 1997	Information Amendment: Clinical
		D. Feigal	On 12/31/96, we submitted an initial written report on stomatitis (Serial No. 287). Attached is the letter that was sent to all participating investigators.
		D. Scott	
B22694	289	Mon, Jan 13, 1997	Information Amendment: Clinical
		D. Feigal	The Investigator's Brochure for cefdinir (Research Report No. 720-03510)has been updated as of 1/3/97 to add the term stomatitis to the list of postmarketing adverse events. The event is also briefly described. An IND safety report on this event was submitted on 12/31/96.
		D. Scott	

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B22694	290	Tue, Mar 11, 1997 D. Feigal D. Scott	Protocol Amendment: New Investigators Regarding Protocol 983-059: New Center 983-059-023 Regarding Protocol 983-060: New Centers 983-060-008 and 983-060-038.
B22694	291	Fri, Mar 14, 1997 D. Feigal P. Chen	Information Amendment: Chemistry, Manufacturing and Controls Reference is made to our IND 34,738, for Cefdinir Capsules and Suspension. This amendment (Research Report No. 939-00690) updates and summarizes the methods and specifications which were described in previous amendments (Serial Nos. 175 and 220) for the 300 mg capsules. The revised specifications are contained in Section 2.0. [redacted] [redacted]. Uniformity of dosage units (USP < 905>) is performed by weight variation since about 86% of the total fill weight is the drug substance.
B22694	292	Fri, May 09, 1997 D. Feigal D. Scott	IND Safety Report: Initial Written Report The adverse event being reported (081-0983-970016) is increased serum amylase (the labeled events of jaundice and hepatic damage were also reported). The events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form (Attachment 1), a 73-year old woman with an upper respiratory tract infection had prolonged hospitalization for jaundice, hepatic damage, and increased serum amylase 5 days after a brief treatment with cefdinir 300 mg/day. The reporting physician considered these events possibly related to cefdinir. There have been no prior reports of increased serum amylase for cefdinir. The Parke-Davis medical reviewer considered the event unlikely to be related to cefdinir because of the temporal relationship to the administration of cefdinir. All participating investigators will be notified of these events via a letter, a prototoype of which is included as Attachment 2.

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B22694	293	Thu, May 15, 1997	IND Safety Report: Initial Written Report
		G. Chikami	We are submitting an initial 10-day safety report (081-0983-970019) on cefdinir. The adverse event being reported is involuntary movements (the labeled event of consciousness disturbance was also reported). The events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form (Attachment 1), a 6-year boy with a history of febrile convulsions experienced involuntary movements and disturbed consciousness on his first day of treatment with cefdinir 40 mg/day for pharyngitis. He was concomitantly receiving mefenamic acid. Both drugs were administered again on Day 2 and the involuntary movements recurred. Both drugs were discontinued. The reporting physician considered the involuntary movements definitely related to cefdinir. We have received no prior reports of this event. The Parke-Davis medical reviewer considered the event possibly related to cefdinir. In accordance with 21 CFR 312.32(c)(1)(i), all participating investigators will be notified of these events via a letter, a prototype of which is included as Attachment 2.
		D. Scott	
B22694	294	Fri, May 23, 1997	Updated Investigator's Brochure, Research Report No. 720-03510
		G. Chikami	The Investigator's Brochure for cefdinir has been updated as of May 9 and May 13, 1997, to add increased serum amylase and involuntary movements to the list of postmarketing adverse events. IND safety reports on these events were submitted on May 9, 1997 (Serial No. 292) and May 15, 1997 (Serial No. 293). Attached for your information and files is the latest version of the Brochure.
		D. Scott	
B22694	295	Thu, Jun 12, 1997	IND Safety Report: Second Follow-up to an Initial Written Report
		G. Chikami	Attached is a MedWatch form that provides follow-up information on a previously reported adverse event (Adverse Event No. 13368). In IND Safety Reports submitted on 6/25/92 and 10/19/92 we reported on a 22-year-old male who participated in Study 983-008, a study of cefdinir in the treatment of skin and skin structure infections. In the original report, bloody diarrhea and appendicitis were reported. Based on sigmoidoscopy, the event was changed to pseudomembranous colitis in the initial follow-up report. However, the investigator has reversed his diagnosis to the originally reported bloody diarrhea based on a pathology report on a biopsy done with the sigmoidoscopy. The report indicated that changes specific for pseudomembranous colitis were not seen.
		D. Scott	
B22694	296	Wed, Aug 13, 1997	Annual Report
		G. Chikami	Annual Report
		D. Scott	

EXHIBIT 11

NDA LOG

IND/NDA/DMF#:	50-739	NDA	Doc Type:	FDA CORRESPONDENCE	11/3/97	Page 1
			SubType:	NDA		
CI#:	983		Sub Date:	9/3/96		
Generic:	Cefdinir		Appr Date:			
Product Name:	Omnicef Capsules					

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B21281		Fri, Aug 16, 1996	Initial Payment of User Fee
		Mellon Bank	As required by the Prescription Drug User Fee Act of 1992, please find enclosed a check [redacted] for a new drug application for Omnicef™ (cefdinir) Capsules, NDA 50-739. This application contains clinical data. For information regarding this NDA submission, please contact: Drusilla Scott, Ph.D. Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road Ann Arbor, MI 48105 Telephone: 313/996-1819 FAX 313/998-3283 Final payment for the NDA will be sent once the first action letter is received.
		B. McManus	
B21281	1	Tue, Sep 03, 1996	Original New Drug Application
		FDA	In accordance with Section 507 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, Parke-Davis is submitting a New Drug Application (NDA) for Omnicef™ (cefdinir) 300 mg Capsules for the treatment of mild to moderate bacterial infections in an outpatient setting. NDA 50-739 was preassigned on May 21, 1996.
		D. Scott	
B22325		Wed, Sep 11, 1996	Received the NDA for Omnicef
		Drusilla L. Scott	Written verification that FDA has received our NDA for Omnicef. Date of application 9/3/96, Date of receipt 9/4/96.
		James D. Bona	
B22325		Tue, Sep 24, 1996	Investigator Information for Division of Scientific Investigations
		M. Thomas	Reference is made to NDA 50-739 for Omnicef™ (cefdinir) Capsules, received by FDA on September 4, 1996. As you requested during the pre-NDA meeting on August 11, 1995, enclosed is clinical investigator information organized by study number for both cefdinir capsules and suspension. Two listings are provided; one for clinical efficacy studies and one for clinical pharmacology/pharmacokinetic studies. Please note that we plan to submit the cefdinir suspension NDA in December, 1996.
		D. Scott	
B22325	2	Tue, Sep 24, 1996	Minor Amendment
		D. Feigal	Reference is made to NDA 50-739 for Omnicef™ (cefdinir) Capsules, received by FDA on September 4, 1996. We are amending the NDA to replace Item 8.15, Principal Investigator List by Study Number, with similar lists submitted to the Division of Scientific Investigations on September 24, 1996. Therefore, please replace pages 1-46 of volume 350 with the attached list; one for clinical efficacy studies and one for clinical pharmacology/pharmacokinetic studies.
		D. Scott	

SubType: NDA

CI#: 983 | Sub Date: 9/3/96

Generic: Cefdinir | Appr Date:

Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No:/
B22325	0	Thu, Oct 10, 1996 P. Colangelo b. Rosen	Diskette of Pharmacokinetics Date Enclosed is a diskette replacing the one previously submitted with the NDA on September 3, 1996, containing pharmacokinetics data.
B22325	3	Mon, Nov 11, 1996 D. Feigal P. Chen	Street Address and Contact Person for the Drug Substance and Product Manufacturers Reference is made to our pending NDA 50-739 and to the telephone call from [redacted] of your Division on November 7, 1996, requesting the street address of the manufacturers of the drug substance and product. Listed below are the contact persons and street addresses for the manufacturers of the drug substance and product.
B22325	4	Wed, Nov 13, 1996 D. Feigal D. Scott	Minor Amendment We are submitting an updated diskette that contains raw biopharmaceutics data from Item 6 in the NDA. [redacted] requested a text description of the data and the updated diskette which contains this information. The diskette has been scanned for all known computer viruses using McAfee Virus Scan version 2.5.2. A paper copy of the parameters described on the diskette, and which was submitted in the original NDA, is included again for convenience of review.
B22647	0	Tue, Nov 19, 1996 M Thomas D Scott	Investigator Information for Division of Scientific Investigations Reference is made to NDA 50-739 for Omnicef™ (cefdinir) Capsules. As you requested during our November 1, 1996 telephone conversation, enclosed is study information for six investigators who participated in the cefdinir program. Requested information is provided in the following order behind each investigator-and-study-specific tab: Protocol and amendments, signed 1572 forms, sample case report forms, and selected data listings per patient. Should you have any questions or comments, please call me at 313/996-1819 or [redacted] at 313/996-7091, or FAX 313/998-3283.
B22716		Tue, Dec 10, 1996 C Debellas D Scott	Pharmacology Summaries on Diskette Enclosed are two replicate diskettes containing the pharmacology, ADME, and toxicology summaries in WordPerfect 6.0a. The diskettes have been scanned for all known computer viruses using Norton Anti-Virus for Windows NT, data file December 9, 1996. I have marked on the attached table of contents which documents are included on the diskette. [redacted] should be able to use these, however, please call me at 313/996-1819 or [redacted] at 313/996-7091 if he has a problem.

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B22707	5	Mon, Dec 16, 1996 D Feigal	Safety Update Attached is the four month safety update to NDA 50-739 Omnicef™ (cefdinir) Capsules. The NDA was submitted on September 3, 1996, and received by FDA on September 4, 1996. The update contains safety information that has become available since the initial submission from ongoing studies, Japanese post-marketing experience, and a completed relative bioavailability study and locally-performed study for French registration purposes. The components are described in more detail in the "Notes to Reviewer" section of the update. The update will be added to the electronic regulatory submission in early January. D Scott
B22716	6	Thu, Dec 19, 1996 D Feigal	General Correspondence: Street Address and Contact Person for the Drug Substance Manufacturer Reference is made to our pending NDA 50-739, the general correspondence submitted on November 11, 1996, and to the telephone call from [redacted] of your Division on December 18, 1996, on the contact person and the street address of the drug substance manufacturer. [redacted] P Chen
B22716	7	Fri, Dec 20, 1996 D Feigal	Minor Amendment: Pharmacology/Toxicology We are submitting a minor pharmacology/toxicology amendment to the NDA to add to the information available on cefdinir impurities/breakdown products (referred to as "cefdinir-related substances" or simply "related substances"). The NDA contained the results of acute toxicity studies in mice on several related substances (Volume 1.12, p. 290). This amendment provides the results of bacterial mutagenicity and in vitro clastogenicity studies on these related substances, as well as the acute intravenous toxicity of RS-1, another related substance. Genetic toxicity studies on RS-1 are ongoing. D Scott

CI#: 983 | Sub Date: 9/3/96
Generic: Cefdinir | Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B22716	8	Tue, Dec 31, 1996 D. Feigal D. Scott	Minor Amendment: Labeling We are amending Items 2.2 (annotated labeling) and 4.4 (proposed package insert) of the NDA for Omnicef™ (cefdinir) Capsules. This NDA was submitted on September 3, 1996, received by FDA on September 4, 1996, and requested approval of cefdinir capsules for six indications in adults and adolescents. An NDA for Omnicef™ (cefdinir) for Oral Suspension, NDA 50-749, was submitted on December 30, 1996, and received by FDA on December 31, 1996. This NDA includes information on the pediatric (suspension) dosage form. Since NDAs that support both dosage forms and both populations have now been submitted, the proposed package insert for cefdinir describes both the capsule and suspension formulations and includes both six adult and four pediatric indications.
B22716	9	Fri, Jan 10, 1997 D. Feigal P. Chen	[redacted] Reference is made to our pending NDA 50-739™ (cefdinir) Capsules and to the telephone call from Dr. Shrikant Pagay of your Division of January 6, 1997, [redacted] Attached is the requested information we received from [redacted]
B22910	10	Fri, Jan 24, 1997 D. Feigal P. Chen	Summary of the Method Validation Package (Item 4 of NDA) Reference is made to our pending NDA 50-739 and to the telephone call from Dr. Shrikant Pagay of your Division on January 22, 1997, requesting information on samples and methods for validation at FDA laboratories. This information is contained in the NDA. For convenience, we have summarized the information from the NDA and provided it below: 1. Drug substance: Methods, Specifications and Validation Reports are contained in Item 4 of the NDA (Volume 10). (see file copy for remainder of list)
B22769	10	Fri, Jan 24, 1997 D. Feigal P. Chen	Summary of the Method Validation Package (Item 4 of NDA) Reference is made to our pending NDA 50-739 and to the telephone call from Dr. Shrikant Pagay of your Division on January 22, 1997, requesting information on samples and methods for validation at FDA laboratories. This information is contained in the NDA. For convenience, we have summarized the information from the NDA and provided it below: (see CBI file for summarization).

CI#: 983 | Sub Date: 9/3/96
Generic: Cefdinir | Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B22910		Fri, Jan 31, 1997 C. Debellas D. Scott	Requested Tables Attached are the tables [redacted] requested from both the adult (983-008) and pediatric (983-013) uncomplicated SSSI studies on cefdinir. I hope they will be helpful in finalizing his review. Please call me at 313/996-1819 [redacted] at 313/996-7091, or FAX 313/998-3283 with any questions.
B22910		Wed, Feb 19, 1997 W. Torres P. Chen	Desk Copy Reference is made to a telephone conference on February 19, 1997, between yourself and [redacted] of Parke-Davis. Parke-Davis submitted a New Drug Application (NDA #50-739) for Omnicef (cefdinir) Capsules. As agreed upon during your February 19, 1997, conversation with Dr. [redacted] we are providing you with a complete copy of the Chemistry, Manufacturing and Controls portion of the Omnicef NDA. Attached, please find copies of Item 3, Volumes 1.2 through 1.9 of NDA 50-739.
B22910		Thu, Feb 20, 1997 P. Chen N. Falcone	NDA Method Validation Letter The FDA will be performing method validation studies on Omnicef 300 mg Capsules, in connection with your NDA 50-739. with your cooperation we can promptly complete this portion of our evaluation of your application. In order to perform the necessary testing, the sample should consist of the following: (see file copy for list).
B22910		Fri, Feb 21, 1997 C. Debellas D. Scott	Microbiology Summary on Diskette In our review meeting of February 12, on the cefdinir NDA's, [redacted] Microbiology Reviewer, requested a WordPerfect version of the Microbiology Summary (Item 7.2, Volume 1.48, NDA 50-739). She also asked that any SAS tables in the summary be submitted in Excel. The WordPerfect 5.2 summary is enclosed on two diskettes, the body on one and appendices on the second. The diskettes have been scanned for all known computer viruses using McAfee Virus Scan version 2.51. The entire document is WordPerfect, therefore no conversion of SAS tables was necessary.
B22910	11	Fri, Feb 21, 1997 D. Feigal D. Scott	Minor Amendment This submission amends two pages of a study report in Item 6 (Human Pharmacokinetics and Bioavailability) of NDA 50-739. This report, RR 744-00305, "A Pharmacokinetic Study of Cefdinir in Patients on Clinical Hemodialysis (Protocol 983-068)" is in Volume 1.45. Pages 35 and 36 were inadvertently replaced in the paper copy by two pages from a different report. The correct pages, Tables 5.1 and 5.2, which describe cefdinir pharmacokinetic parameters on Day 1 and Day 2 post-dose, are attached. The pages have also been faxed to [redacted] to forward to [redacted]

CI#: 983 Sub Date: 9/3/96
Generic: Cefdinir Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./
B22910	12	Mon, Mar 03, 1997 D. Feigal D. Scott	Minor Amendment We are amending Item 13.3 of NDA 50-739, the debarment certification required by the Generic Drug Enforcement Act of 1992. We understand that the phrase "To the best of its knowledge" must be deleted from the statements to avoid an appearance of qualification. The amended certification follows this letter.
B22910	13	Tue, Mar 04, 1997 D. Feigal D. Scott	90-Day Meeting Minutes On February 12, 1997, we held a "90-day" meeting with members of the cefdinir review team. We thank your staff for taking the time to discuss the status of the review, the NDA and ERS components they found most useful, and those components that could be improved upon in the future. Two discrete action items resulted from the meeting: (see file copy for additional information)
B22910		Fri, Mar 07, 1997 H. Coffman P. Chen	Method Validation Samples We are sending you the following samples and documents for the method validations of our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension. (see file copy for list)
B22910		Fri, Mar 07, 1997 N. Falcone P. Chen	Method Validation Samples We are sending you the following samples and documents for the method validations of our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension. (see file copy for list)
B22910		Mon, Mar 10, 1997 C. Debellas D. Scott	Abbreviated Summary Tables As requested by [redacted], enclosed are abbreviated summary tables created from the case report tabulations. These tables are for the two otitis media studies, 983-10 and 983-11. For each study, the treatment groups are listed in the following order: Cefdinir 14 mg/kg QD, Cefdinir 7 mg/kg BID, Augmentin 13.3 mg/kg TID.
B22910		Mon, Mar 10, 1997 Paul Chen Harry D. Coffman	Methods Validation testing acknowledgement Methods Validation testing acknowledgement for Omnicef Capsules and Powder for Oral Suspension.

CI#: 983 Sub Date: 9/3/96
Generic: Cefdinir Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B22910		Tue, Mar 18, 1997 D. Opalenik W. Rosen	Case Report Forms Enclosed are two diskettes which contain the case report forms (CRFs) for one of the patients associated with the cefdinir submission. The file associated with CRFs for this patient was found to be corrupted on the server here in Ann Arbor. As such, the file is likely corrupted on the Parke-Davis server at the FDA. The diskettes have been scanned for all known computer viruses using McAfee for Windows 95.
B22418		Mon, Mar 31, 1997 C. Debellas D. Scott	Requested Information Attached are the "key parameters" abstracted from the case report tabulations for the studies in lower respiratory tract infections, as requested by Dr. Holli Hamilton. Could you please forward these to her. As described in the tentative schedule I gave you on February 21, 1997, following studies are included: Lower Respiratory Tract Infections Studies 983-004 and 983-026, Pneumonia Study 983-019, Supportive pneumonia (pediatric) Study 983-005, AECB Study 983-038, Acute bronchitis Study 983-016, Mixed LRTI's
B12248		Wed, Apr 16, 1997 C. Debellas D. Scott	Desk Copy: Requested Information The enclosed volumes contain microbiological and clinical laboratory data on 92 patients in Study 983-007 (10-day adult pharyngitis). These pages were inadvertently not scanned in as part of the electronic case report forms in Study 983-007. The data are in the database and were entered on the case report tabulations.
B23282	14	Fri, Apr 25, 1997 D. Feigal S. Brennan	Response to the Draft Deficiency Letter of the Environmental Assessment Section Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ Capsule and Powder for Oral Suspension and to the draft deficiency letter of the Environmental Assessment section (EA) of the NDAs on March 13, 1997. The combined EA for Omnicef Capsule and Powder for Oral Suspension has been separated into two individual documents for capsules and powder for oral suspension, respectively as suggested. They are included as Attachments 1 and 2. The non-confidential versions are also included as Attachments 3 and 4, respectively.

CI#: 983 | Sub Date: 9/3/96
Generic: Cefdinir | Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B23282	15	Tue, May 06, 1997 D. Feigal	Response to Request for Information At the request of [redacted], Supervisory Medical Officer, we have re-analyzed the efficacy and safety data for cefdinir studies in which either [redacted] participated. We have examined the efficacy parameters for each study at the test-of-cure visit in the evaluable populations specific to each study, both with and without these investigators' data. (All adverse events and drug-associated adverse events were also reviewed in each population.). Finally, for each study, we have listed the microbiological eradication rate by pathogen for all sites, for sites except [redacted] and for these investigators' sites alone. Attachments 1-6 contain the information for the studies. A floppy diskette containing a Word document is enclosed for each study, and can be given to the appropriate reviewer. The diskettes have been scanned for all known computer viruses using Norton Anti-Virus for Windows NT.
		D. Scott	
B23282		Fri, May 09, 1997 B. Duvall-Miller	Requested Copies of Chromatograms As requested by the inspector in the Division of Scientific Investigations, enclosed are chromatograms from eight subjects (22%) from Study 983-066, A Single-Dose Bioequivalence Study Comparing 300 mg Cefdinir Capsules used in Clinical Studies to Market-Image 300 mg Cefdinir Capsules. The chromatograms are presented as they were run in batches for Subjects 5 and 6; 13 and 14; 21 and 22; and 27 and 28.
		D. Scott	
B23348		Tue, May 13, 1997 B. Duvall-Miller	Requested Copy of Presentations In accordance with the message I left, enclosed are copies of earlier presentations and an upcoming presentation to the National Committee on Laboratory Standards (NCCLS) for cefdinir. [redacted] requested this information for her review and to facilitate FDA-NCCLS congruence on microbiologic susceptibility.
		D. Scott	
B23348		Wed, May 14, 1997 B, Duvall-Miller	Response to FDA Request for Information As requested by [redacted] enclosed are the microbiology raw data from the cefdinir sinusitis study 983-006. The microbiology data were generated by a central laboratory, and printouts were inadvertently not scanned into the electronic NDA submission. The forms for Site 23 actually are in the electronic submission as standard case reporting forms (CRFs) as the data from this site only came from the local laboratory.
		D. Scott	
B23394		Fri, May 30, 1997 B. Duvall-Miller	SSSI Reanalysis: Desk Copies As we discussed, enclosed are three desk copies of the reanalysis of Study 983-013, a pediatric study of cefdinir versus cephalexin in the treatment of uncomplicated skin and skin structure infections. [redacted]
		D. Scott	

CI#: 983 | Sub Date: 9/3/96
Generic: Cefdinir | Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B23394	16	Mon, Jun 02, 1997 D. Feigal S. Brennan	Response to the Chemistry Reviewer's Draft Deficiency Letter Reference is made to our pending NDA 50-739 for Omnicef7 Capsules and to the draft deficiency letter of the Chemistry, Manufacturing and Controls sections of the NDA on April 29, 1997, from [redacted] of your Division. For convenience of review, the comments are repeated in italics followed by our response.
B23394		Tue, Jun 03, 1997 B. Duvall-Miller D. Scott	Sinusitis Study Reanalysis: Desk Copies As we discussed, enclosed are three desk copies of the reanalysis of Study 983-006, a pediatric study of cefdinir versus amoxicillin/clavulinic acid in the treatment of acute maxillary sinusitis. [redacted]
B23395		Thu, Jun 05, 1997 B. Duvall-Miller D. Scott	Reanalyses of Pharyngitis Studies: Desk Copies As we discussed, enclosed are three desk copies of the reanalyses of Studies 983-051 and 983-056, two pediatric studies of cefdinir versus penicillin in the treatment of pharyngitis. [redacted]
B23395	17	Wed, Jun 11, 1997 D. Feigal S. Brennan	Update of Stability Data Reference is made to our pending NDA 50-739 for Omnicef Capsules. We are updating the NDA with recent stability results at 12 and 18 months (Appendix 15 of the NDA) in Attachment 1 and a statistical analysis report (including a diskette) as Attachment 2. The diskette has been scanned for all known computer viruses.
B23395	0	Wed, Jun 11, 1997 B. Duvall-Miller D. Scott	Reanalysis of Suspenion Safety Studies: Desk Copies As we discussed, enclosed are three desk copies of the reanalysis of safety data for cefdinir suspension. [redacted]
B23395		Mon, Jun 16, 1997 B. Duvall-Miller D. Scott	Reanalysis of Capsule Safety Studies: Desk Copies As we discussed, enclosed are three desk copies of the reanalysis of safety data for cefdinir capsules. [redacted] The desk copies are for [redacted] (since there are no microbiology data, we have not included a copy for [redacted]). A diskette is also included for [redacted] or the summary and tables, which are available in WordPerfect. Only the two laboratory tables copied directly from the NDA ISS are not in WordPerfect. The diskette has been scanned for all known computer viruses using Norton Anti-Virus for Windows NT.

CI#: 983 | Sub Date: 9/3/96
Generic: Cefdinir | Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B23476	18	Mon, Jun 23, 1997 G. Chikami D. Scott	Amendment to a Pending Application: Clinical Reanalyses This submission amends NDA 50-739 for cefdinir capsules to include the results of efficacy and safety reanalyses of several studies, and of all capsule and suspension safety, [redacted]
B23475	19	Mon, Jun 30, 1997 G. Chikami D. Scott	Revision to Clinical Amendment On June 23, 1997 (Reference No. 18), we submitted an amendment to the NDA that in[redacted] participated in (except for otitis media, which will be submitted in the near future). The safety and efficacy data were reanalyzed without these investigators' data.
B23475	20	Tue, Jul 01, 1997 G. Chikami D. Scott	Amendment: Microbiology Information This amendment includes scattergrams of MIC versus zone diameter for the Haemophilus spp. summarized in the NDA, as requested by[redacted] June 11, 1997 (Attachment 1). In addition, two research reports are attached. These support the suggested microbiological changes in labeling as proposed in the working copy sent to Ms. Duvall-Miller for your June 19 labeling meeting. The reports are as follow: RR 720-03830 entitled, "Reassessment of Quality Control Limits for Disk Diffusion Susceptibility Tests with 5 mg Cefdinir Disks versus S. Aureus ATCC 25923," [redacted] dated December 16, 1996 (Attachment 2) RR 720-03866 entitled, "Criteria for Interpreting Disk Susceptibility Tests of Streptococcus Species Against Cefdinir," by[redacted] June 20, 1997 (Attachment 3)
B23475	21	Mon, Jul 07, 1997 G. Chikami D. Scott	Amendment: Clinical Information This submission to NDA 50-739 replies to information conveyed by[redacted] on the results of the Division's cefdinir labeling meeting of June 19, 1997. During that meeting, three proposed indications for cefdinir were discussed; acute maxillary sinusitis, uncomplicated skin and skin structure infections (SSSI), and pharyngitis/tonsillitis.
B23475	23	Tue, Jul 08, 1997 G. Chikami P. Chen	Name Change Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, respectively. We were notified by our contract manufacturer[redacted]

CI#: 983 Sub Date: 9/3/96
Generic: Cefdinir Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B23475	22	Tue, Jul 08, 1997	Amendment: Clinical Information
		G. Chikami	This amendment to NDA 50-739 contains a reanalysis of the safety and efficacy information from the otitis media study 983-010, [redacted] Desk copies of this submission are included for [redacted] The diskette, which is included for Dr. Hamilton, contains summary information and selected tables from Attachment A in WordPerfect. (Diskette has been scanned for any known viruses using [redacted]
		D. Scott	
B23475	24	Wed, Jul 09, 1997	Corrections of Stability Update
		G. Chikami	Reference is made to our pending NDA 50-739 for Omnicefâ (cefdinir) Capsules and to the stability update (Ref. No. 17) submitted on June 11, 1997. It has come to our attention that the Form 356h is incorrect and there are pages missing in Attachments 1 and 2 of the June 11, 1997 submission.
		S. Brennan	
B23510	25	Mon, Jul 21, 1997	Amendment: Clinical Information
		G. Chikami	This submission to NDA 50-739 replies to a July 7, 1997, telephone request by [redacted] o provide evidence of treatment arm balance in pivotal lower respiratory tract infection studies (LRTI) for cefdinir. Specifically [redacted] sked that pulmonary diagnoses by treatment arm and distributions of clinically evaluable patients and microbiologically and clinically evaluable patients by treatment arm and site be provided for pivotal LRTI studies.
		D. Scott	
B23510	26	Tue, Jul 22, 1997	Correction
		G. Chikami	There was an error which appeared in the NDA Volume 9 Appendix 18 (Specifications for the HDPE Bottle and Closure) Page 92. The specification of Loss on Drying for the cotton coil was 7.0% Maximum. However, the cotton coils used in the NDA stability batch were released by our contract manufacturer, [redacted] nder their specification of 8.0% Maximum. The excellent stability data of the capsules generated through 18 months demonstrates that the difference should post no concern on the product quality.
		P. Chen	
B23510	0	Wed, Jul 23, 1997	Listings of Patients with Predisposing Conditions
		B. Duvall-Miller	Reference is made to our pending NDA for Omnicef Ó (cefdinir) capsules and to a July 22, 1997, conversation between [redacted] of your Division and [redacted] f Parke-Davis regarding listings of patients with predisposing conditions for the cefdinir commonly-acquired pneumonia trials. As requested by [redacted] we are providing the requested information as a desk copy for her convenience.
		D. Scott	

CI#: 983 Sub Date: 9/3/96
Generic: Cefdinir Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B23510		Tue, Aug 05, 1997	User Fee date extended to December 4, 1997
		Drusilla Scott	We acknowledge receipt of the June 24, 1997 and June 23 1997 amendment to your NDA for Omnicef Capsules. We consider this a major amendment, therefore the user fee clock has been extended 3 months.
		Gary K. Chikami	
B23510	27	Fri, Aug 29, 1997	Second Safety Update
		G. Chikami	Attached is a second safety update to NDA 50-739, OmnicefÒ (cefdinir) Capsules. As this information also pertains to NDA 50-749 for OmnicefÒ (cefdinir) for Oral Suspension, a letter is being simultaneously submitted to that NDA which requests incorporation by reference. The date for FDA action on this application has changed from September 4, 1997, to December 4, 1997, as a result of a major amendment submitted on June 23, 1997 (Ref. No. 18). This amendment contained requested reanalyses of NDA studies without data from two investigators under review by FDA's Division of Scientific Investigation (DSI).
		D. Scott	
B23695	28	Wed, Sep 10, 1997	Minor Amendment: Pharmacology/Toxicology
		G. Chikami	We are submitting a minor pharmacology/toxicology amendment to the NDA to add to the information available on cefdinir impurities/breakdown products. The acute intravenous toxicity and genotoxic potential of cefdinir and related substances (RS) II, III, V, VII, XI, XIII, and XV have been summarized previously in the original NDA,and in an amendment (Ref. No. 7, submitted December 20, 1996). Results of the acute intravenous toxicity of additional cefdinir-related substances RS-1, RS IV, and RS VIII were also summarized. The results of the bacterial mutagenicity and in vitro clastogenicity assays for these compounds are included in the current amendment. Two additional cefdinir-related substances, RS D and RS E, were assessed for acute intravenous toxicity and genotoxic potential and results are also presented in this amendment.
		D. Scott	
B23702	29	Wed, Sep 10, 1997	Amendment: Draft Labeling
		G. Chilami	Please refer to our pending applications NDA 50-739 for Omnicef Ò (cefdinir) Capsules and NDA 50-749 for OmnicefÒ (cefdinir) for Oral Suspension. Enclosed are cefdinir labeling materials for our meeting on September 23, 1997, and your internal meeting on September 18, 1997. Per my discussions with Ms. Beth Duvall-Miller, the following items are included, each behind the corresponding tab number.
		D. Scott	
B23702	30	Thu, Sep 18, 1997	Amendment: Clinical Information
		G. Chikami	Amendment: Clinical Information
		D. Scott	

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B23702		Tue, Oct 07, 1997 Drusilla Scott Gary Chikami	FDA completed review FDA has completed review of the human pharmacokinetics and bioavailability section of our submissions and have the following recommendations and comments. See file copy for complete information.
B23702	31	Wed, Oct 08, 1997 G. Chikami D. Scott	Meeting Minutes On September 23, 1997, members of your Division and representatives from Parke-Davis had an initial meeting to discuss proposed labeling for cefdinir capsules and suspension. We appreciate the opportunity to have had this productive meeting. Parke-Davis' minutes from that meeting are enclosed. Eleven desk copies are enclosed for [redacted] for distribution to each attendee. We would appreciate any comments on these minutes and a copy of the Division's minutes as soon as they are available.
B23702	32	Thu, Oct 16, 1997 G. Chikami S. Brennan	Final Draft Container Labels Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, respectively. Attached, please find the final draft container labels for these two products. Attachment 1 is the label for the 300 mg Capsule. The labels for suspension product 6 oz bottle (100 mL after constitution), 4 oz bottle (60 mL after constitution), and 30 cc bottle (5 mL after constitution) are provided as Attachments 2, 3, and 4 respectively. This version has incorporated comments and recommendations from the Agency. In addition, we have revised the storage condition of the constituted suspension to include "or store refrigerated, 2-8EC (36-46EF)". The stability data supporting this statement was included in the August 27, 1997, submission (Ref. No. 10). The constitution direction for the 30 cc bottle (physician sample) has also been changed from "Add 2 teaspoon of water" to "Add 4 mL (approximately 1 teaspoonful) of water". The change in volume of water added to constitute the powder is in line with other physician samples of similar products on the market.

CI#: 983 | Sub Date: 9/3/96
Generic: Cefdinir | Appr Date:
Product Name: Omnicef Capsules

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B23702	33	Mon, Oct 20, 1997	Responses to Recommendations on Human Pharmacokinetics and Bioavailability Section
		G. Chikami	Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, to the teleconferences of July 15 and 17, 1997, and to the communication from you of October 7, 1997, respectively, regarding recommendations for the human pharmacokinetics and bioavailability sections of the NDAs. We agree to change the dissolution specification for the capsules from a Q value of 75% at 30 minutes to a Q value of 80% at 30 minutes. For the powder for oral suspension, the dissolution method and recommended specification were submitted on August 13, 1997 (NDA 50-749 Ref. No. 9). The method uses USP Apparatus II at 50 rpm in 900 mL pH 6.8 phosphate buffer at 37°C. The specification is a Q value of 80% at 30 minutes. The validation report for this method was submitted on September 29, 1997 (NDA 50-749 Ref. No. 12).
		P. Chen	
B23702	34	Mon, Oct 27, 1997	Amendment: Draft Labeling
		G. Chikami	Please refer to our pending new drug applications for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, the labeling discussion held on September 23, 1997, and our minutes of that meeting submitted to NDA 50-739 on October 8, 1997 (Ref. No. 31). Please also refer to your letter of October 7, 1997, which made recommendations and comments on dissolution testing (Items 1 and 2) and the human pharmacokinetics section of the labeling (separate item). Items 1 and 2 were responded to on October 20, 1997 (NDA 50-739 Ref. No. 33 and NDA 50-749 Ref. No. 14). In this amendment, we are submitting draft labeling based on our meeting of September 23, 1997. We are thereby also responding to the labeling comments in your October 7, 1997 letter, as we discussed these recommendations in the meeting. The current working draft labeling, dated October 27, 1997, is Attachment 1; changes from the Agency draft of September 22 are outlined in Attachment 2; and the September 22 draft itself is Attachment 3. Attachment 4 is our rationale for not including the ß-lactamase negative ampicillin-resistant strains of H. influenzae in the labeling.
		D. Scott	

IND/NDA/DMF#:	50-739 NDA	**Doc Type:**	FDA CONTACT
		SubType:	NDA
CI#:	983	**Sub Date:**	9/3/96
Generic:	Cefdinir	**Appr Date:**	
Product Name:	Omnicef Capsules		

Barcode	Date To: From:	RE/Contents
B22349	Thu, Sep 26, 1996 Beth Duvall-Miller Drusilla L. Scott, Ph.D	Ms. Duvall-Miller forwarded, through Sue Belskus, a complete list of reviewers for NDA 5 The reviewers for cefdinir have been assigned.
B22349	Tue, Oct 01, 1996 Beth Duvall-Miller Bill Rosen	To determine why WordPerfect Version 5 documents were unaccessable. Access to read-only Version 5 documents from WordPerfect Version 6 continues to indiscriminately plague cefdinir reviewers.
B22349	Wed, Oct 09, 1996 Beth Duvall-Miller Bill Rosen	To relate results of experiments conducted with WordPerfect Version 7. WordPerfect Version 6.1 users cannot open write protected Version 5 files from the DOS prompt or from Windows '95 Explorer. Installation of a software patch provided by WordPerfect has had limited success.
	Mon, Oct 21, 1996 Dave Opalenik Marilyn Royle	To load a maintenance update to the cefdinir Electronic Regulatory Submission (ERS) an Marilyn Royle, with the assistance of Perry Caldwell and Pauline Cheng, loaded a new electronic table of contents, additional WordPerfect files, and additional SAS data to the Parke-Davis ERS server at the FDA.
B22349	Fri, Nov 01, 1996 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	Division of Scientific Investigations requested study information for six investigators in the The Division of Scientific Investigations has requested site information and data from six investigators who participated in the cefdinir program. Data listings were requested in a specific format.
B22349	Mon, Nov 04, 1996 Carmen Debellas Drusilla L. Scott, Ph.D	The chemist wants the street addresses for the manufacturer of drug substance and drug The chemist wants the street addresses for the manufacturer of drug substance and drug product, and the addresses for the facilities which do packaging and testing, including any contractors.
B22349	Fri, Nov 08, 1996 Shrikant Pagay, Ph.D. P. Chen	To find out the contact person and street address for the manufacturer of drug substance Dr. Pagay called and asked for information of contact person and street address for each manufacturing and testing site for drug substance and product for requesting pre-approval inspections.
B22349	Fri, Nov 08, 1996 Holli Hamilton, MD Bill Rosen	To provide an introduction to the Parke-Davis Electronic Regulatory Submission (ERS) to Bill Rosen provided Holli Hamilton with an introduction to the Parke-Davis ERS. Carl Tidwell worked with Alaka Chakravarty to facilitate access to SAS datasets on the UNIX server from PC SAS through SAS/Connect. Bill also met with Andy Bonwit and David Ross to answer questions related to the system.

SubType: NDA

CI#: 983 Sub Date: 9/3/96

Generic: Cefdinir Appr Date:

Product Name: Omnicef Capsules

Barcode	Date / To: / From:	RE/Contents
B22349	Thu, Nov 14, 1996 Carmen Debellas Drusilla L. Scott, Ph.D	Possible pediatric sinusitis indication As was done recently in an efficacy supplement for loracarbef, the Division will consider approving an indication for pediatric sinusitis if we include support for this (primarily literature and a description of the relationship between the formulations) in the suspension NDA.
B22349	Tue, Nov 26, 1996 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	Request for information on pivotal studies. Dr. Thomas in Clinical Investigations requested study design and summary information on all pivotal studies conducted in North America. This information was faxed to him.
B22349	Thu, Dec 05, 1996 David Ross, M.D., Ph. Bill Rosen	To support Dr. Ross's presentation of the Parke-Davis Electronic Regulatory Submission (Bill Rosen provided training to Aloka Chakravarty and Andy Bonwit regarding how to use the Parke-Davis ERS. He also supported Dr. David Ross who delivered a demonstration of the system to FDA Administrators at an internal conference.
B22349	Wed, Dec 11, 1996 Dave Opalenik Bill Rosen	Jim Blank had deleted some software from his PC which prevented him from accessing th Oracle and eXceed software were restored to Jim Blank's PC following an attempt to recover space on his hardisk.
B22349	Tue, Dec 17, 1996 Dave Opalenik Bill Rosen	To confirm dates for loading the FDA server with cefdinir safety update and suspension s January 6, 1997 was confirmed as the date we would load the FDA server with information related to the cefdinir safety update and the cefdinir suspension submission. On January 7, new software will be loaded to the PCs of the cefdinir reviewers. A system upgrade will be performed in March.
B22349	Wed, Dec 18, 1996 Shrikant Pagay, Ph.D. P. Chen	To confirm the street address and contact person of [redacted] Dr. Pagay called and wanted to confirm the contact person and street address of [redacted]
	Fri, Jan 03, 1997 Dr. Rupa Viraraghava Bill Rosen	Rupa called to report that she was unable to access the cefdinir Electronic Regulatory Su [redacted]
B22349	Fri, Jan 03, 1997 Dr. Rupa Viraraghava Bill Rosen	Rupa called to report that she was unable to access the cefdinir Electronic Regulatory Su Multiple network problems at the server and client level were preventing some FDA reviewers from accessing the cefdinir Electronic Regulatory Submission. [redacted]

SubType: NDA

Cl#: 983 | Sub Date: 9/3/96

Generic: Cefdinir | Appr Date:

Product Name: Omnicef Capsules

Barcode	Date / To: / From:	RE/Contents
B22349	Mon, Jan 06, 1997 Dave Opalenik Pauline Cheng	To install the 4 month safety to the Cefdinir Capsule Electronic Regulatory Submission an With the assistance of Marilyn Royle of Scientific Information Engineering and Pramo Chepuri of the Ann Arbor Data Center, Pauline Cheng successfully loaded all electronic information pertaining to the Cefdinir Capsule Safety Update and the Cefdinir Suspension NDA to the Parke-Davis server at the FDA.
B22349	Tue, Jan 07, 1997 Shrikant Pagay, Ph.D. P. Chen	To request street addresses of [redacted] [redacted] starting material, intermediate(s) and the final product of cefdinir drug substance.
B22349	Tue, Jan 07, 1997 Mr. Shirley Isbel Drusilla L. Scott, Ph.D	[redacted]
B22349	Wed, Jan 08, 1997 James Blank, PhD. Drusilla L. Scott, Ph.D	To discuss summary listings for SSSI Studies. Dr. Jim Blank, Medical Reviewer for the SSSI studies, has asked for a summary listing of patients and major outcome measures for the adult (983-008) and pediatric (983-013) SSSI Studies. The tables cannot be produced with the ERS. They can be produced in Programming in a few weeks due to the structure of the database, and will be sent to Dr. Blank when completed.
B22349	Wed, Jan 08, 1997 Carmen Debellas Bill Rosen	Carmen called to report that Roopa Virarghavan could not access SQLAssist from her PC Roopa Viraraghavan was unable to connect to SQLAssist through the Parke-Davis ERS system due to an error in the DNS on the FDA network. Dave Fry of Desktop Computing Services assisted Dave Opalenik in resolving the problem.
B22349	Tue, Jan 14, 1997 James Blank, PhD. Drusilla L. Scott, Ph.D	Faxed table of key parameters from the patient summaries. Dr. Blank finds the abbreviated patient summary tables acceptable, and we will program and forward tables from Studies 983-008 and 983-013 in two weeks. A concern about consistency in the determination of clinical evaluability was clarified, based on the criterion that a patient was not clinically evaluable if baseline pathogens were resistant to cefdinir or comparator.
B22349	Tue, Jan 14, 1997 Holli Hamilton, MD Drusilla L. Scott, Ph.D	Unable to locate Appendix A.4 in the report for 983-004 (RR 720-03456), US pneumonia Dr. Holli Hamilton could not find Appendix A.4 in RR 720-034546 (983-004, US pneumonia) in the CANDA. This appendix describes how the clinical score was determined. We located the appendix in both the NDA and CANDA; however, "Appendix 04.A.1st" was displayed at the top of every page of the previous appendix, A.3., which probably made the search confusing. This should have been in the bottom left-hand corner, but several documents were generated with this type of error before it was detected and corrected in future documents. As this may confuse other reviewers as to where they are in the document, we need to be aware of this and be able to direct reviewers to the desired location.

IND/NDA/DMF#:	50-739 NDA	Doc Type:	FDA CONTACT
		SubType:	NDA
CI#:	983	Sub Date:	9/3/96
Generic:	Cefdinir	Appr Date:	
Product Name:	Omnicef Capsules		

Barcode	Date / To: / From:	RE/Contents
B22349	Fri, Jan 17, 1997 Shrikant Pagay, Ph.D. L. Lescosky	FDA contacted Parke-Davis to inquire about samples of Omnicef Capsules. Dr. Pagay called to request the lot numbers for Cefdinir samples which are available for the FDA validation lab.
B22349	Wed, Jan 22, 1997 Dave Opalenik Pauline Cheng	To install the cefdinir suspension ERS on Andy Bonwit's and Janice Soreth's PCs. To res During our standard monthly visit, Pauline Cheng successfully installed the cefdinir suspension ERS on Andy Bonwit's PC. At Andy's request, she reset his system passwords. Janice Soreth's PC was still unavailable for the software installation. Pauline was unable to resolve the problems that Roopa was having accessing the ERS server over the network.
B22349	Wed, Jan 29, 1997 Holli Hamilton, MD Bill Rosen	Holli called to inquire about remote connection to our system as she will be working from [redacted] She desired to remotely connect to our server at the FDA. This technology has not yet been deployed at the FDA. She was provided with a portable PC with which she could [redacted]
B22349	Tue, Feb 04, 1997 Carmen Debellas Bill Rosen	Carmen called to inform me that Jim Blank was unable to bring up the Parke-Davis Electr Jim Blank and all other cefdinir reviewers are unable to connect to the Parke-Davis ERS. This is due to a script file developed and executed by FDA personnel which replaced all users oracle.ini and tsnames.ora files.
B22349	Fri, Feb 14, 1997 Dave Opalenik Bill Rosen	To correct database access problems created by a logon script that had been run over th Dave Fry, Dave Opalenik, and Bill Rosen worked together to correct problems created by a logon script that was executed over the FDA network. The logon script had rendered the Parke-Davis ERS inoperable over the FDA network. Dave, Dave, and Bill were joined by Perry Caldwell and jointly they assisted with preparations for a training class conducted by Nancy Brucken and Russ Newhouse of Clinical Reporting Systems. The training class introduced the cefdinir reviewers to the Clinical Summary System.
B22349	Wed, Feb 19, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To obtain two tables missing from a report. Two pages of tables from the hemodialysis report were missing from the FDA copy of the NDA. The correct pages had been replaced by "correction" pages from another report, which also contained the replacement pages. The PDM and CBI paper copies, and the ERS and Documentum versions of the hemodialysis report contained the tables, and had not been modified. The correct pages were faxed to FDA and will be formally submitted as an amendment.
B22349	Thu, Feb 20, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To request key parameter tables for Dr. Hamilton. Dr. Holli Hamilton liked the key parameter tables we had programmed for the SSSI studies, and requested similar tables for the studies she is responsible for. After internal discussion, a schedule for completion was faxed back to FDA.

IND/NDA/DMF#:	50-739	NDA	Doc Type:	FDA CONTACT
			SubType:	NDA
CI#:	983		Sub Date:	9/3/96
Generic:	Cefdinir		Appr Date:	
Product Name:	Omnicef Capsules			

Barcode	Date / To: / From:	RE/Contents
B22349	Thu, Feb 20, 1997 Dave Opalenik Bill Rosen	To confirm dates for the upgrade of the Parke-Davis Electronic Regulatory Submission (E Perry Caldwell will upgrade the Parke-Davis ERS server at the FDA during the first week of March. He will be assisted by Andy Dowswell of the AADC and Bill Rosen of SIE. The server will be down for a minimum of 3 days.
B22349	Fri, Feb 21, 1997 Nicholas Falcone L. Lescosky	FDA contacted Parke-Davis to request samples cefdinir drug substance and Omnicef Cap FDA is requesting samples of Omnicef Capsules and Suspension for their validation lab.
B22349	Mon, Feb 24, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	Request for monitoring reports fo[redacted]. DSI is investigating[redacted]or two pediatric pharyngitis studies. Dr. Thomas requested, and was sent, the monitoring reports for these studies.
B22349	Tue, Feb 25, 1997 Janice Soreth, M.D. Drusilla L. Scott, Ph.D	To estimate pediatric SSSI outcome without data from one investigator [redacted]Since he contributed a substantial number of patients to the pediatric SSSI study, she asked us to look at efficacy with and without his data. Our primary efficacy analyses were quite similar with and without the Fiddes data, in part because the efficacy rates are so high.
B22349	Wed, Feb 26, 1997 Dr. Matthew Thomas Tim Cunniff, Pharm.D	Request for additional monitoring reports fo[redacted] Dr. Thomas called requesting any additional monitoring records (informal notes, evaluations) for[redacted]sites for Protocols 983-51 and 983-56. If there is no additional information, a statement to this effect should be provided.
B22349	Thu, Feb 27, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	[redacted] [redacted] The NDAs will be amended to remove this phrase.
	Fri, Feb 28, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	To send additional monitoring information. In response to Dr. Thomas' request for more monitoring inform[redacted] [redacted]ated some documents that were not part of the monitoring reports, but provided some additional information. These were forwarded to Dr. Thomas.
B22349	Fri, Feb 28, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	Test In response to Dr. Thomas' request for more monitoring informati[redacted] [redacted]ocated some documents that were not part of the monitoring reports, but provided some additional information. These were forwarded to Dr. Thomas.
B22349	Fri, Feb 28, 1997 Dave Opalenik Bill Rosen	Dave Opalenik sent e-mail to inform Bill Rosen that Jim Blank was unable to use SQLAss Jim Blank was unable to access the Oracle database via SQLAssist on the Parke-Davis server at the FDA. It was determined that Jim's PC had been improperly configured for the FDA network. Dave Opalenik corrected the configuration and Jim's access was restored. Dave also indicated that he believed an upgrade to Version 5 of the Hummingbird Exceed software would be beneficial.

SubType: NDA

CI#: 983 Sub Date: 9/3/96

Generic: Cefdinir Appr Date:

Product Name: Omnicef Capsules

Barcode	Date / To: / From:	RE/Contents
	Mon, Mar 03, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	Request for two CRF's from Study 983-51-11. Dr. Thomas requested CRFs from patients 46 and 65 [redacted]-51 (10-day pediatric pharyngitis).
B22349	Mon, Mar 03, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	Request for two CRFs from Study 983-051-14 Dr. Thomas requested CRFs from patients 46 and 65 fr[redacted] (10-day pediatric pharyngitis).
B22349	Fri, Mar 07, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	To see if he received "lost" documents sent to Florida. As of March 7, Dr. Thomas had not received the monitoring materials we sent to the Florida office on February 28. These will be re-faxed to his Washington office on March 10.
B22349	Fri, Mar 07, 1997 Janice Soreth, M.D. Drusilla L. Scott, Ph.D	Discussed pediatric SSSI and other studies' outcome without data from one investigator Dr. Janice Soreth, Supervisory Medical Officer, [redacted] parameters computed with and without his data for all studies he participated in.
B22349	Fri, Mar 07, 1997 Janice Soreth, M.D. Drusilla L. Scott, Ph.D	Request for additional information on [redacted] Upon Dr. Soreth's request, [redacted] been sent to FDA. [redacted]
B22349	Thu, Mar 13, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To transmit draft deficiency letter on environmental assessment. A deficiency letter on the EA was received. There do not appear to be significant scientific deficiencies.
B22349	Tue, Mar 25, 1997 Sousan Altaire, PhD Drusilla L. Scott, Ph.D	To request NCCLS submissions on cefdinir breakpoints. Dr. Altaire requested the Parke-Davis submissions to the NCCLS; FDA hopes to reach concordance with NCCLS' recommendations for breakpoints.
B22349	Tue, Mar 25, 1997 Dr. Roopa Viraraghav Drusilla L. Scott, Ph.D	Question on possible discrepancy in number of investigators in pharyngitis studies. There appeared to be a discrepancy in the NDA in the number of investigators participating in pharyngitis studies. Two of the three tables in question were correct, although somewhat difficult to follow; the third table was incorrect. The NDA had been amended with a correct and more complete investigator listing, which showed there was no discrepancy.
B22349	Tue, Mar 25, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To obtain clinical study and case report tabulations page counts for GAO. The GAO requested total page numbers in the NDA for clinical pharmacology and efficacy studies, and for case report tabulations. The respective number of pages are: 7357; 21,429; 73,409.

SubType: NDA

CI#: 983 Sub Date: 9/3/96

Generic: Cefdinir Appr Date:

Product Name: Omnicef Capsules

Barcode	Date To: From:	RE/Contents
B22349	Thu, Apr 03, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To send minutes from 90-day meeting. The FDA's minutes of the 90-day meeting were received, and are consistent with ours.
	Thu, Apr 03, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To send minutes from 90-day meeting. The FDA's minutes of the 90-day meeting were received, and are consistent with ours.
B22349	Fri, Apr 04, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To characterize clinical data in NDA [redacted] As part of a CDER exercise to evaluate the usefulness of study reports submitted in NDAs, the cefdinir NDA clinical pharmacology and clinical efficacy study reports were categorized according to CDER-supplied definitions.
B22349	Fri, Apr 11, 1997 Dr. Roopa Viraraghav Drusilla L. Scott, Ph.D	To determine location of microbiological data in CRFs in Study 983-007. The microbiology and clinical laboratory data is not included in the CRFs (provided electronically only) for Study 983-007. The medical reviewer is unable to "quality assure" a random subset of patients from the study. Paper copies for the 92-patient subset should be sent as soon as possible, as her review is being delayed.
B22349	Mon, Apr 14, 1997 Dr. Roopa Viraraghav Tim Cunniff, Pharm.D	To provide patient identification codes corresponding to random sample numbers request Patient identification codes corresponding to random sample numbers for Protocol 983-7 were provided to FDA. Dr. Viraraghaven had requested this information so that she could review the microbiology data captured in the case report forms for these patients. Dr. Viraraghaven made one additional request; she would like to receive a hard copy of the lab data for these patients as well.
B22349	Tue, Apr 15, 1997 Dr. Roopa Viraraghav Drusilla L. Scott, Ph.D	To send information on how clinical outcome was assigned. I left a message for Dr. Viraraghavan, explaining how patients received clinical outcome assignments in Study 983-007 when investigator and sponsor assessments were not concordant.
B22349	Thu, Apr 17, 1997 Dr. Roopa Viraraghav Drusilla L. Scott, Ph.D	To determine whether all pharyngitis patients in Study 983-007 had clinical outcome asse Parke-Davis assigned a clinical outcome to all 983-007 pharyngitis patients, not only those the investigator assigned as non-assessable.
	Fri, Apr 25, 1997 Janice Soreth, M.D. Drusilla L. Scott, Ph.D	To describe safety and efficacy tables to be generated with and without selected investiga I faxed Dr. Soreth the tables and analyses we plan to forward [redacted]
B22349	Tue, Apr 29, 1997 Carmen Debellas Tim Cunniff, Pharm.D	To provide Chemistry Reviewer's comments. The Chemistry Reviewer's comments on the NDA for cefdinir capsules were faxed to Parke-Davis (fax attached). The CSO asked for a projected timeframe for our response.

CI#: 983 Sub Date: 9/3/96
Generic: Cefdinir Appr Date:
Product Name: Omnicef Capsules

Barcode	Date / To: / From:	RE/Contents
B22349	Thu, May 01, 1997 Beth Duvall-Miller Janeth L. Turner	Ask when revised data sets will be available. The requested data sets will be available tomorrow. Drusilla will call Janice Soreth to finalize details of shipment.
B22349	Thu, May 01, 1997 Shrikant Pagay, Ph.D. P. Chen	To obtain clarifications on comments in the draft deficiency letter and brief him about our f I called Dr. Pagay to clarify some questions in the deficiency letter and to inform him that some of the questions raised regarding the drug substance are DMF issues.
B22349	Fri, May 02, 1997 Janice Soreth, M.D. Drusilla L. Scott, Ph.D	To send reanalysis results from Study 983-013. We faxed the reanalyses of efficacy and adverse event data for Study 983-013, pediatric SSSI, to the Supervisory Medical Officer for [redacted] The rest of the study results will be sent on Monday, May 5.
B22349	Thu, May 08, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	Request for chromatograms from Study 983-066 (Capsule Bioequivalence) Chromatograms from 20% of the subjects who participated in the capsule bioequivalence study must be forwarded immediately for DSI inspection. The original request was misdirected to the wrong fax number.
B22349	Mon, May 12, 1997 Andrew Bonwit, M.D. Drusilla L. Scott, Ph.D	To find microbiology CRF pages from sinusitis studies. The microbiology CRF pages from the US sinusitis study are missing in the CANDA. The reviewer agreed to accept paper copies for only the patients with the pathogens requested in the labeling.
B22349	Wed, May 14, 1997 Janice Soreth, M.D. Drusilla L. Scott, Ph.D	[redacted] [redacted] Each reviewer will request what is needed by the end of the week. A rapid response is required to maintain the review progress, which has been impeded by the investigator problems and reorganization of the Divisions within ODE IV.
	Thu, May 15, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	[redacted] [redacted] The request on pharyngitis, which, suggests a current need for a revised efficacy and safety summary.
B22349	Thu, May 15, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	[redacted] [redacted] The request on pharyngitis, which remains to be clarified, suggests a current need for a revised efficacy and safety summary.
B22349	Tue, Jun 10, 1997 Sousan Altaire, PhD Tim Cunniff, Pharm.D	To inquire about H. influenzae susceptibility breakpoints. Dr. Altaie called to seek clarification regarding H. influenzae susceptibility breakpoint data presented to the NCCLS and included in the NDA for cefdinir capsules. She was informed that data presented at NCCLS summarized US central lab values only; the NDA includes all data. Dr. Altaie will recommend intermediate and resistant breakpoints based on the NDA data that was not available to NCCLS. In addition, Dr. Altaie requested that scattergrams of MIC vs. zone diameter data for H. influenzae strains summarized in the NDA be submitted as soon as possible.

IND/NDA/DMF#:	50-739	NDA	Doc Type:	FDA CONTACT	
			SubType:	NDA	
CI#:	983		Sub Date:	9/3/96	
Generic:	Cefdinir		Appr Date:		
Product Name:	Omnicef Capsules				

Barcode	Date To: From:	RE/Contents
B22349	Wed, Jun 11, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To request information on cefdinir indications and dosage in Japan and England. Indications and dosing regimes for cefdinir in Japan and England were faxed in response to a request.
B22349	Tue, Jun 17, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To send response to Biopharmaceutics Reviewer's question. A response to the Biopharmaceutics Reviewer's questions about the effect of transposed data on our conclusions regarding the most important determinant of cefdinir elimination was faxed to the project manager. Our conclusion that renal function is the primary determinant was not affected by the transposition.
B22349	Wed, Jun 18, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To provide assessment of Nomenclature Committee and current thoughts of Division on tr As part of the NDA review, the FDA Nomenclature Committee recommended against the tradename "Omnicef" for cefdinir based on its similarity to "Omnipen". The Division has a further concern about the potential for anaphylaxis if a penicillin-allergic patient is misprescribed Omnipen. I forwarded a response that included all previous FDA/PD correspondence on the tradename.
B22349	Wed, Jun 18, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To send working copy of package insert with adverse event and laboratory abnormality nu A working copy of the labeling generated from the modified database that resulted from removal of the Fiddes/Iravani data was forwarded to FDA to facilitate their labeling review.
	Fri, Jun 20, 1997 Regina Alivisatos Drusilla L. Scott, Ph.D	To relay information on indications discussed at FDA labeling meeting The Division reviewed and recommended approval of sinusitis, SSSI, and pharyngitis, although not with all pathogens requested, and with a conclusion that cefdinir was equivalent, but not superior to, penicillin in the treatment of pharyngitis. Any challenges we want to make to these recommendations should be sent to Ms. Duvall-Miller as soon as possible.
B22349	Fri, Jun 20, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To relay information on indications discussed at FDA labeling meeting. The Division reviewed and recommended approval of sinusitis, SSSI, and pharyngitis, although not with all pathogens requested, and with a conclusion that cefdinir was equivalent, but not superior to, penicillin in the treatment of pharyngitis. Any challenges we want to make to these recommendations should be sent to Ms. Duvall-Miller as soon as possible.
B22349	Thu, Jun 26, 1997 Andrew Bonwit, M.D. Drusilla L. Scott, Ph.D	To ask about clinical outcome in MITT patients. Dr. Bonwit asked if he could obtain clinical outcome data in the MITT population in both sinusitis studies. We indicated that we could obtain these numbers if he wished, although PD does not assess this. Rather, microbiological outcomes are determined to more fully assess antimicrobial efficacy. Dr. Bonwit will call again if he decides that he wants the clinical outcome data in this population.
B22349	Thu, Jun 26, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To relay findings of no significant impact on Environmental Assessment. A finding of no significant impact (on the environment) statement has been issued for cefdinir capsules and suspension.

IND/NDA/DMF#:	50-739	NDA	Doc Type:	FDA CONTACT
			SubType:	NDA
CI#:	983		Sub Date:	9/3/96
Generic:	Cefdinir		Appr Date:	
Product Name:	Omnicef Capsules			

Barcode	Date / To: / From:	RE/Contents
B22349	Mon, Jul 07, 1997 Holli Hamilton, MD Drusilla L. Scott, Ph.D	To request evidence of treatment arm balance in pivotal lower respiratory tract infection (The medical reviewer requested a presentation of several patient populations by treatment arm for each of the four pivotal LRTI studies. Statistical analysis may be needed to ensure balance by treatment.
B22349	Wed, Jul 16, 1997 Dave Opalenik Sue Belskus	To update the Electronic Regulatory Submission for Omnicef Capsules at the FDA. On July 16-17, 1997, Sue Belskus updated the Electronic Regulatory Submission for Omnicef Capsules.
B22349	Tue, Jul 22, 1997 Beth Duvall-Miller Tim Cunniff, Pharm.D	To inform Parke-Davis of divisional meeting regarding the proposed trademark Omnicef The Division does not have a strong argument to prevent PD from using the trademark Omnicef. However, FDA still has concerns with the use of Omnicef and will likely seek a Phase 4 commitment from PD prior to approval which would require the company to track and follow-up on medication errors. If a substantial number of errors are observed, PD would have to change the tradename.
B22349	Wed, Jul 23, 1997 Beth Duvall-Miller Tim Cunniff, Pharm.D	To reschedule PD/FDA cefdinir labeling meeting. The PD/FDA cefdinir labeling meeting has been rescheduled for September 23, 1997, 930-1130 am.
B22349	Tue, Jul 29, 1997 Dave Opalenik Bill Rosen	Parke-Davis Electronic Regulatory Submission (ERS) software will need to be installed on Dave Fry of Desktop Computing Services in Ann Arbor will work with Ellen Messersmith of the FDA Department of Infomation Systems Design to load the Parke-Davis Electronic Regulatory Submission (ERS) software onto a new PC for Jim Blank.
B22349	Mon, Aug 04, 1997 Dave Opalenik Dave Fry	To install the Parke-Davis Electronic Regulatory Submission (ERS) system software on a Dave Fry met with Dave Opalenik and Ellen Messersmith to load the Parke-Davis Electronic Regulatory Submission (ERS) system to a new PC for Jim Blank. Dave also met with Holli Hamilton to resolve problems she was having with WordPerfect Version 6.1 on the portable PC she is using to access the ERS.
B22349	Thu, Aug 21, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To discuss what FDA labeling comments we will receive before September 23rd meeting. FDA will meet to further discuss our proposed labeling one week before the joint meeting on September 23. We should submit an updated labeling package by September 10; this submission should address issues we know about by September 4. Any major new issues that arise in the FDA internal meeting will not have to be resolved at the September 23 meeting; a later meeting can be scheduled.
B22349	Tue, Sep 02, 1997 Dave Opalenik Alison Buno	To update for cefdinir Electronic Regulatory Submission (ERS) on the Parke-Davis server Sue Belskus and I updated the Electronic Regulatory Submission on the Parke-Davis server at the FDA to include the second safety update and amendment number 25 for cefdinir.
B22349	Wed, Sep 03, 1997 Holli Hamilton, MD Alison Buno	To determine why Remote Access Services (RAS) was not operating properly for Holli Ha Sue Belskus and Alison Buno met with Holli Hamilton to assist with remote access problems she was encountering with her laptop. We were unable to establish a cause for the problem.

Best Available Copy

IND/NDA/DMF#:	50-739	NDA	Doc Type:	FDACONTACT	11/3/97	Page 11
			SubType:	NDA		
CI#:	983		Sub Date:	9/3/96		
Generic:	Cefdinir		Appr Date:			
Product Name:	Omnicef Capsules					

Barcode	Date / To: / From:	RE/Contents
	Thu, Sep 04, 1997	[redacted]
	Holli Hamilton, MD Alison Buno	Alison Buno assisted Holli Hamilton with several different procedures to resolve a connectivity problem. These included resetting passwords, changing initialization files, and running the check disk utility.
	Thu, Sep 04, 1997	[redacted]
	Holli Hamilton, MD Alison Buno	Alison Buno assisted Holli Hamilton with several different procedures to resolve a connectivity problem. These included resetting passwords, changing initialization files, and running the check disk utility.
	Thu, Sep 04, 1997	[redacted]
	Holli Hamilton, MD Alison Buno	Alison Buno assisted Holli Hamilton with several different procedures to resolve a connectivity problem. These included resetting passwords, changing initialization files, and running the check disk utility.
B22349	Thu, Sep 04, 1997	[redacted]
	Holli Hamilton, MD Alison Buno	Alison Buno assisted Holli Hamilton with several different procedures to resolve a remote connectivity problem to the Parke-Davis server at the FDA. These procedures included resetting passwords, changing initialization files, and running the check disk utility.
B22349	Wed, Sep 17, 1997	To locate Appendices C in the study report for 983-16, the dose-ranging study in lower re
	Beth Duvall-Miller Drusilla L. Scott, Ph.D	The medical reviewer could not locate the C appendices for the study report for the LRTI dose-ranging study, 983-16. The C and D appendices were not in the paper copy of the NDA, but were in the CANDA. Since they covered several hundred pages of SAS output that is difficult to read on screen, I suggested that the reviewer look at the title of each appendix, and that we then forward paper copies if she wants most or all of the appendices. [She has requested copies of Appendices C16, and C19-22]
B22349	Thu, Sep 18, 1997	To send draft labeling comments.
	Beth Duvall-Miller Drusilla L. Scott, Ph.D	FDA faxed their comments on the draft cefdinir labeling.
B22349	Fri, Oct 03, 1997	Discuss Omnicef Suspension 4 ounce bottle and final bottle labels.
	Shrikant Pagay, Ph.D. Paul Chen	Dr. Pagay has accepted the 4 ounce bottle for Omnicef Suspension. He would like to see the final draft bottle label before we finalize it.
B22349	Tue, Oct 14, 1997	To send draft otitis media Clinical Studies section for cefdinir labeling.
	Beth Duvall-Miller Drusilla L. Scott, Ph.D	A draft Clinical Studies section for otitis media in the labeling was faxed to FDA for their internal meeting on the indication.
B22349	Wed, Oct 15, 1997	To relay results of FDA meeting on the otitis media indication.
	Beth Duvall-Miller Drusilla L. Scott, Ph.D	The pathogens S. pneumoniae, H. influenzae, and M. catarrhalis will be granted for the otitis media indication. FDA will forward a revised Clinical Studies section.

IND/NDA/DMF#:	50-739	NDA	**Doc Type:**	FDA CONTACT	
			SubType:	NDA	
CI#:	983		**Sub Date:**	9/3/96	
Generic:	Cefdinir		**Appr Date:**		
Product Name:	Omnicef Capsules				

Barcode	Date / To: / From:	RE/Contents
B22349	Thu, Oct 23, 1997 Beth Duvall-Miller Drusilla L. Scott, Ph.D	To notify us why the FDA otitis media labeling could not be sent. FDA is uncertain about the approvability of the cefdinir BID dosing regimen for otitis media, primarily because of the low eradication rate for S pneumoniae. Approvability of the QD regimen is not an issue.
B22349	Tue, Oct 28, 1997 Carmen Debellas Tim Cunniff, Pharm.D	To request teleconference to discuss Omnicef labeling submitted to FDA on October 27, A teleconference to discuss Omnicef labeling will be held with FDA on October 30, 1997.
	Thu, Oct 30, 1997 Carmen Debellas Tim Cunniff, Pharm.D	RD/FDA teleconference to discuss clinical outcome data for otitis media studies. FDA asked why the clinical cure rate for the international clinical trial (Protocol 983-11) was so much higher than that reported for the domestic clinical trial (Protocol 983-10). Noting that baseline clinical scores were higher in the international trial than they were in the domestic trial, the Medical Officer wondered if the improved category influenced the reported clinical cure rates, and asked that TOC clinical scores be provided for Protocols 983-10 and -11.

EXHIBIT 12

ASSIGNMENT RECORDATION

Assignment Of Application

WHEREAS, I (WE) Takao Takaya, Hisashi Takasugi, Takashi Masugi, Hideaki Yamanaka, and Kohji Kawabata, of No. 1-5-87, Suimeidai, Kawanishi-shi, Hyogo, Japan, No. 1-14-33, Hamaguchi-nishi, Suminoe-ku, Osaka-shi, Osaka, Japan, No. 3-10-11, Hachizuka, Ikeda-shi, Osaka, Japan, No. 2-77-19, Kuauha-Nakanoshiba, Hirakata-shi, Osaka, Japan, and No. 1-7-31, Oriono, Sumiyoshi-ku, Osaka-shi, Osaka, Japan, respectively, have invented certain new and useful improvements in: 7-Substituted-3-vinyl-3-cephem compounds and processes for production of the same, for which an application for Letters Patent was executed on September 12, 1983, and

WHEREAS, Fujisawa Pharmaceutical Co., Ltd. (hereinafter referred to as "ASSIGNEE") having a place of business at: No. 3, 4-chome, Doshomachi, Higashi-ku, Osaka, Japan, is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefor in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

I (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assignment and sale not been made.

Further, I (WE) agree that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

The undersigned hereby grant(s) the firm of Oblon, Fisher, Spivak, McClelland & Maier, P.C. of 1755 S. Jefferson Davis Highway, Crystal Square, Arlington, Virginia 22202 the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

EXECUTED AT: Osaka, Japan

Date: September 12, 1983 — Tafao Takaya
(Signature of Inventor)

Date: September 12, 1983 — Kisashi Takasuyo
(Signature of Inventor)

Date: September 12, 1983 — Tabashi Masuyo
(Signature of Inventor)

Date: September 12, 1983 — Hideaki Yamanaka
(Signature of Inventor)

Date: September 12, 1983 — Koku Kawabata
(Signature of Inventor)

RECORDED
PATENT & TRADEMARK OFFICE
SEP 18 1995

ACTING COMMISSIONER OF
PATENTS & TRADEMARKS

OBLON, FISHER, SPIVAK, McCLELLAND & MAIER, P.C.
PATENT & TRADEMARK ATTORNEYS
CRYSTAL SQUARE FIVE – SUITE 400
1755 S. JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202